CLOFARABINE
NDA 21-673

ONCOLOGIC DRUG ADVISORY COMMITTEE
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TABLE OF CONTENTS

Section **Page**

TABLE OF CONTENTS (continued)

Section **Page**

TABLE OF CONTENTS (continued)

Section **Page**

LIST OF APPENDICES

TABLES INCLUDED IN THE TEXT

TABLES INCLUDED IN THE TEXT (continued)

TABLES INCLUDED IN THE TEXT (continued)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation:	**Definition**
AE(s)	adverse event(s)
ALL	acute lymphocytic leukemia
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration x time curve
BMT	bone marrow transplant
BSA	body surface area
CI	confidence interval
CK-MB	creatine kinase MB fraction
CL	total systemic clearance
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
Cmax	maximum serum concentration
CNS	central nervous system
COG	Children's Oncology Group
CR	complete remission
CRp	complete remission in the absence of platelet recovery
CTC	Common Toxicity Criteria
dCK	deoxycytidine kinase
dCyd	deoxycytidine
DLTs	dose-limiting toxicities
EEAP	emergency expanded access program
ECHO	echocardiogram
EP	European Pharmacopaeia
FAB	French American British
FDA	U.S. Food and Drug Administration
G-CSF	granulocyte colony stimulating factor
GI_{50}	growth inhibition
GM-CSF	granulocyte-macrophage colony stimulating factor
hOAT	human organic anion transporter
HSCT	hematopoietic stem cell transplant
I	improvement
IND	Investigational New Drug Application
IP	intraperitoneal
IRRP	Independent Response Review Panel
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (continued)

Abbreviation:	Definition
ITT	intent-to-treat
IV	intravenous
IVI	intravenous infusion
KPS	Karnofsky Performance Status
LV	left ventricular
LVSD	left ventricular systolic dysfunction
MDACC	M. D. Anderson Cancer Center
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Affairs
MTD	maximum tolerated dose
MUD	matched unrelated donor
MUGA	multiple gated acquisition scan
NCI	National Cancer Institute
NCI CTC	National Cancer Institute Common Toxicity Criteria
NDA	New Drug Application
NEC	not elsewhere classified
NOS	not otherwise specified
OR	overall remission
OS	overall survival
PBSCT	peripheral blood stem cell transplant
PD	progressive disease
PE	pericardial effusion
PK	pharmacokinetics
PO	orally
PR	partial remission
RBC	red blood cell
SAE	serious adverse event
SC	subcutaneous
SCID	severe combined immunodeficient
SD	stable disease
SIRS	systemic inflammatory response syndrome
TBI	total body irradiation
USP	United States Pharmacopeia
Vdss	volume of distribution at steady-state
WBC	white blood cell (count)

EXECUTIVE SUMMARY

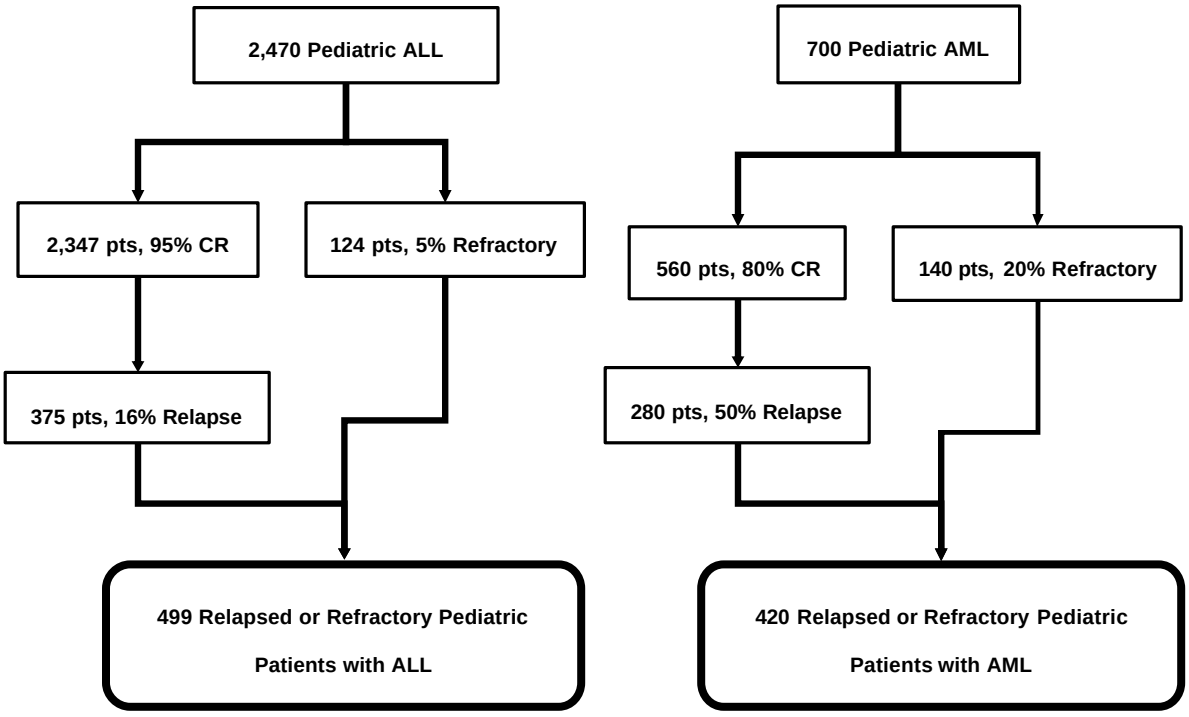
PREFACE

ILEX decided to accelerate the pediatric development program in advance of the adult development program because of the impressive activity demonstrated by clofarabine in the Phase I pediatric study of these highly refractory ALL and AML patients. The decision to move into 2 parallel Phase II studies followed discussions with the U.S. Food and Drug Administration (FDA) and outside pediatric oncologists. While the development program of clofarabine in pediatric and adult patients continues, the data from the 2 pivotal Phase II pediatric studies support the filing of this New Drug Application (NDA).

BACKGROUND

Leukemia is the most common cancer in the pediatric population; acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) are the two most common types of leukemia in pediatric patients. Each year in the United States, approximately 2000 children are diagnosed with ALL, 500 with AML, and <100 with chronic myeloid leukemia (CML). Current multi-agent therapeutic regimens cure as many as 70% of pediatric patients with ALL and 50% of pediatric patients with AML. However, the rest of the patients do not achieve long-term remission or cure with currently available therapies. The figure below helps illustrate the pediatric acute leukemia population as estimated by a cancer surveillance program, SEER.

US Incidence of Pediatric Acute Leukemias



Source: Cancermetric/SEER

Today's pediatric patients with recurrent or refractory acute leukemia are heavily pretreated and, typically, their disease has become cross resistant to available therapies. Many have already undergone hematopoietic stem cell transplantation (HSCT). As a consequence of their prior therapies, these patients usually have substantial comorbid conditions. Due to advances in therapy, this modern-day population of children with relapsed or refractory acute leukemia is strikingly different from the published literature of clinical studies targeting the relapsed pediatric acute leukemia population. Thus, this population represents a group of patients with an unmet medical need that has not been addressed in previous controlled clinical studies. Therefore, comparison of the results of ILEX's Phase II studies with other therapies is extremely difficult. Key differences between the population in the ILEX Phase II trials and the pediatric population in the literature are as follows:

- Many published results are from small studies (<20 patients) and were investigator studies conducted at a single site.

- Earlier Phase II studies imposed strict limits on the number of prior regimens that patients could have received, often treating patients in first relapse. In addition, these studies rarely included patients who had undergone prior transplant.

- Almost all published results are based exclusively on investigator assessment of response and did not involve an independent review of efficacy.

- Definitions of response terms (complete, partial, etc) varied from study to study and were not often defined in detail. In many studies, complete remission (CR) was defined as <5% bone marrow blasts, but without any reference to recovery of peripheral blood counts.

- Many of the studies conducted were not well controlled with rigorous data collection, monitoring, and reporting.

- "Death on study" was not always clearly defined.

CLOFARABINE PHARMACOLOGY

Clofarabine represents a novel oncolytic that has demonstrated activity in patients with advanced—multiply recurrent or refractory—leukemia. Clofarabine is a nucleoside analogue that differs from similar approved agents (ie, fludarabine and cladribine) in the following respects:

- The efficiency (Vmax/Km) of phosphorylation of clofarabine by deoxycytidine kinase (dCK) is equal to or greater than that of its natural substrate deoxycytidine (dCyd), and significantly greater than that of cladribine (~3-4 times greater) and fludarabine (~25 times greater).

- Clofarabine has higher retention and greater accumulation in the lymphocytes of chronic lymphocytic leukemia (CLL) patients than does cladribine.

- Clofarabine and cladribine produce apoptosis through a direct and indirect pathway, whereas fludarabine produces apoptosis only through an indirect pathway.

- The inhibitory potency of clofarabine triphosphate on ribonucleotide reductase was similar to that of cladribine triphosphate, 10 times greater than fludarabine triphosphate, and 100 times greater than gemcitabine triphosphate.

- The inhibition of DNA chain elongation by polymerase α by clofarabine triphosphate was similar to that of fludarabine triphosphate but greater than that of cladribine triphosphate.

- Peak concentration of clofarabine triphosphate in CLL and AML cells was 3- to 4- fold higher than that for cladribine triphosphate.

- The intracellular half life ($t_{1/2}$) was longer for clofarabine triphosphate (7.3 hours) than for cladribine triphosphate (4.3 hours).

- The 48-hour concentration of clofarabine triphosphate was more than twofold greater than that measured for cladribine.

These preclinical data demonstrate that clofarabine, while structurally similar to the approved nucleoside analogues, has unique pharmacological properties that impart distinct potential pharmacologic advantages.

Preclinical studies have demonstrated the activity of clofarabine against multiple types of hematologic and solid tumor malignancies. Because of the efficacy of clofarabine in preclinical models, further development was undertaken so that trials in humans could be initiated. Clofarabine induced the expected adverse effects on lymphoid tissue, bone marrow, gastrointestinal tract, and testes of mice, rats, and dogs. Clofarabine at very high doses (in acute studies, 150 mg/m^2/day given as a bolus injection) resulted in cardiac lesions in the rat only. These studies supported a starting dose for Phase I trials of 15 mg/m^2/day for 5 days.

CLOFARABINE DEVELOPMENT STRATEGY

Nearly all pediatric oncology treatments were originally investigated in and approved for use in adults, which may have resulted in a substantial delay in getting these therapies to children. According to the Pediatric Oncology Subcommittee meeting on 17 October 2002, there was a median delay of 6 years between the initiation of the first adult Phase I study and the initiation of a first pediatric Phase I study of the following drugs: gemcitabine, paclitaxel, cladribine, irinotecan, temozolomide, docetaxel, tretinoin, topotecan, and imatinib. This may also have resulted in less than optimal application (eg, dose, schedule, understanding of toxicities, etc) of these drugs in the pediatric population since many were

used "off label" after approval for adults and before well-controlled studies were conducted in pediatric patients.

In contrast, ILEX engaged in the parallel development of clofarabine in pediatrics and adults, identifying potential differences in dosing, tolerance, and pharmacokinetics between these 2 populations.

DOSE SELECTION AND PHASE I RESULTS

A Phase I study (DM93-036) of clofarabine was initiated in adults with hematologic and solid tumor malignancies on a daily × 5 schedule. Approximately 18 months after initiation of the Phase I adult study, a Phase I pediatric study (ID99-383) of clofarabine in patients with hematologic malignancies was begun.

This Phase I study in pediatric patients (ID99-383)—an open-label, non-randomized, dose-escalation study—was conducted in patients with hematologic malignancies (ALL and AML) who had failed standard therapy or for whom no such therapy existed. Doses were escalated from 11.25 mg/m^2/day to 70 mg/m^2/day. The dose-limiting toxicities (DLTs) in this study were grade 4 hyperbilirubinemia and grade 3 maculopapular rash (observed in 1 patient each in the 70 mg/m^2/day group) and the maximum tolerated dose (MTD) was determined to be 52 mg/m^2/day. Additional clinical pharmacology studies that supported the 52 mg/m^2/day dose for Phase II studies included the following:

- Plasma clofarabine concentrations increased with increasing dose.
- Intracellular clofarabine triphosphate concentrations increased with increasing dose, were highest at the end of infusion, and remained quantifiable 24 hours after the start of infusion.
- DNA synthesis was inhibited in leukemic cells at the end of infusion, but had a 10% to 50% recovery by the next dose (ie, breakthrough DNA synthesis). Only at the MTD (52 mg/m^2/day) and higher was DNA synthesis inhibition maintained throughout the dosing interval.

Although not designed to be an efficacy trial, the Phase I study nevertheless explored response in the 25 pediatric patients. The investigator determined there were 5 patients (20%) with CR, 3 patients (12%) with partial remission (PR), and 7 patients (28%) with "improvement." Seven of the 25 patients (28%) proceeded to transplant after treatment with clofarabine. To enable comparison with the Phase II studies of clofarabine, ILEX requested that an Independent Response Review Panel (IRRP) retrospectively review data for the patients assessed as CR by the investigator, using the Phase II response criteria employed in the pivotal studies. The IRRP determined there were 2 patients with CR, 1 patient with complete remission in the absence of platelet recovery (CRp), and 2 patients with PR.

EFFICACY OF PEDIATRIC PHASE II STUDIES

Because of the striking activity of clofarabine in a patient population with no other curative options, and after discussions with the FDA, ILEX launched 2 parallel Phase II non-randomized, open-label, single-arm studies in relapsed and refractory pediatric patients with ALL and AML. The patients in both studies, CLO-212 for patients with ALL and CLO-222 for patients with AML, were treated at 52 mg/m^2/day $\times$ 5 days each cycle.

The primary objective of these studies was to determine the overall remission (OR) rate (CR + CRp) of clofarabine in pediatric patients with refractory or relapsed ALL (CLO-212) or AML (CLO-222). A Fleming two-stage design was used in both studies. For purposes of establishing a stopping rule, a target OR rate of 40% was selected by ILEX prior to beginning enrollment. No prespecified minimum OR rate was agreed upon with the FDA for establishing efficacy. The FDA stated that identification of a clinically meaningful response rate would be a review issue.

Secondary objectives included documenting the rate of CR, CRp, and PR; duration of remission and overall survival (OS); safety profile and tolerability of clofarabine for this population and dosing regimen; and the pharmacokinetic profile and intracellular pharmacology and metabolism of clofarabine in selected patients. In addition, data on patients who proceeded to transplant, including post-transplant survival, were collected and analyzed to ascertain the clinical benefit of single-agent clofarabine treatment. After

discussion with the FDA, post-transplant data were collected for duration of remission and survival.

It should be noted that there were two types of PRs:

- PR with an M1 marrow that does not qualify for CR or CRp, usually involving lack of absolute neutrophil count (ANC) or platelet recovery.
- PR with complete disappearance of circulating blasts, an M2 bone marrow and appearance of normal progenitor cells,

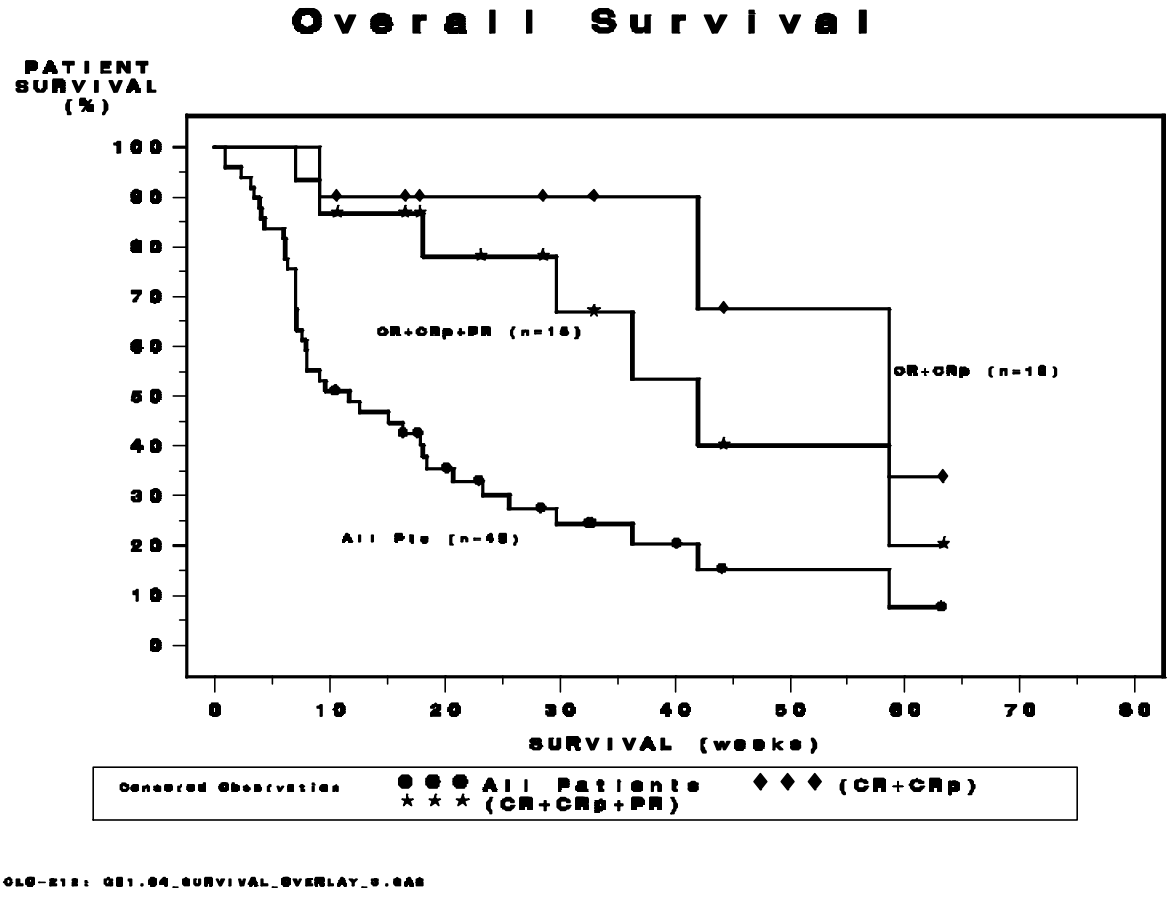
Although patients with an M2 marrow and patients with an M1 marrow were both classified as a PR, there is a qualitative difference between these two types of PRs. A patient who is a PR by definition but has an M1 marrow could potentially achieve a response of CRp or CR if given time for ANC recovery. This type of PR may also increase the likelihood of successful transplant, due to the additional cytoreduction. Patients who are a PR but have an M2 bone marrow may also benefit from proceeding to transplant, especially for patients with AML.

The bulleted list below summarizes the key efficacy results by study for the 49 patients in CLO-212:

- The OR rate (CR + CRp) for patients with ALL was 20% (6 CR, 4 CRp; 95% CI: 10% to 34%); the response rate for patients achieving at least a PR (CR + CRP + PR) was 31% (95% CI: 18% to 45%).
- Thirty of the 49 patients (61%) in this study were refractory to their most recent prior regimen. The OR rate (CR + CRp) for patients with ALL who were refractory to the most recent prior therapy was 17% (3 CR, 2 CRp); the response rate in this population for patients achieving at least a PR (CR + CRP + PR) was 23%.
- The median duration of remission for patients with ALL who achieved an OR (CR + CRp) was 20.2 weeks. The median duration of remission for patients with ALL who achieved at least a PR (CR + CRP + PR) was 9.7 weeks.
- The median duration of remission for patients with ALL who were refractory to the most recent prior therapy who achieved an OR (CR + CRp) was 6.1 weeks. The median duration of remission in this subpopulation for patients with ALL achieving at least a PR (CR + CRP + PR) was 4.6 weeks.

- The median survival for patients with ALL who achieved an OR has not yet been reached as 7 of the 10 patients with ALL were still alive at data cutoff. The median survival for patients with ALL who achieved at least a PR (CR + CRP + PR) was 42.0 weeks. The median survival for all patients with ALL was 11.7 weeks.

The Kaplan-Meier survival curves for CLO-212 are presented below by response group and for all patients.



CLO-212: GS1.04_SURVIVAL_OVERLAY_0.SAS

The bulleted list below summarizes the key efficacy results of the 35 patients with AML (CLO-222).

- The OR rate (CR + CRp) for patients with AML was 3% (0 CR, 1 CRp; 95% CI: 0% to 15%), although there were other clinical benefits achieved, such as substantial cytoreduction allowing patients to proceed to transplant. The response rate for patients who achieved at least a PR (CR + CRP + PR) was 26% (95% CI: 12% to 43%). In addition, 1 patient in this study had a response that the IRRP confirmed as a CR; however, the patient was deemed not evaluable because he had only 12% blasts at study enrollment, below the minimum for study entry. He also had a chloroma with 100% blasts that resolved following treatment with clofarabine.

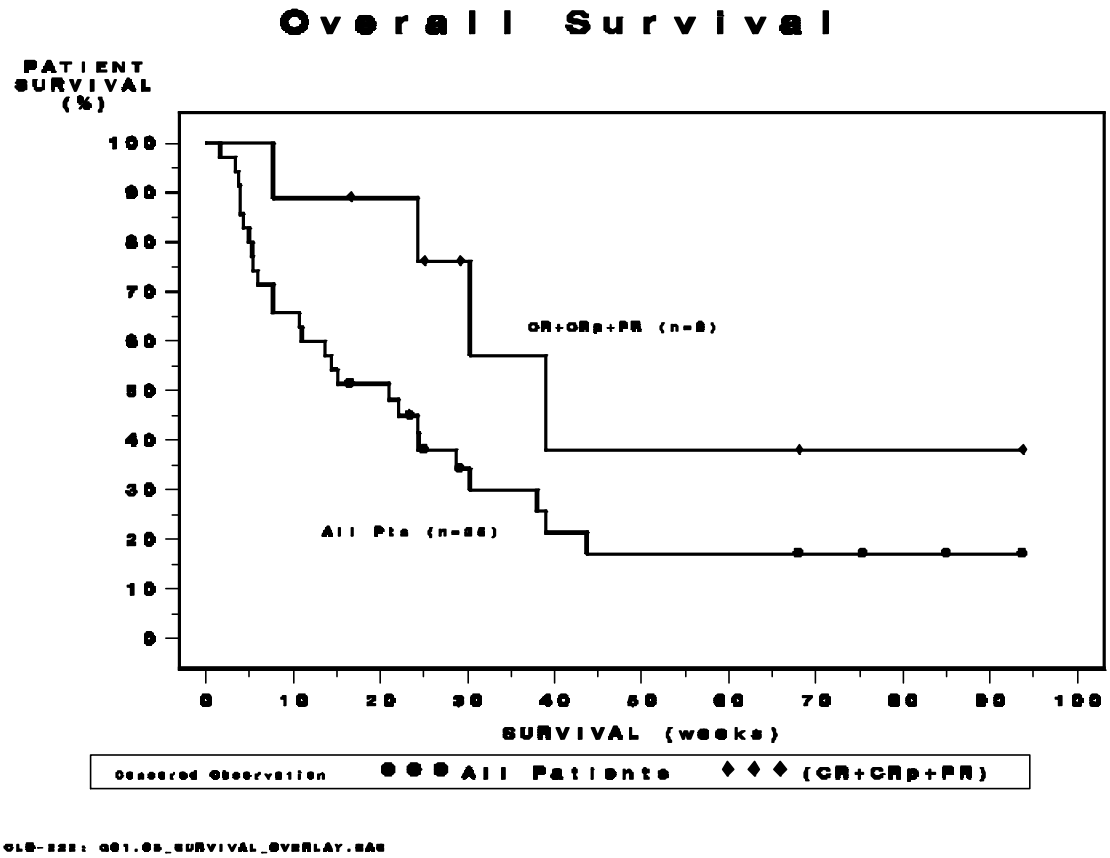
- Twenty-two of the 35 patients (63%) in this study were refractory to their most recent prior regimen. The OR rate (CR + CRp) for patients with AML who were refractory to the most recent prior therapy was 0%; the response rate in this subpopulation for patients achieving at least a PR (CR + CRP + PR) was 18%.

- The duration of remission for the 1 patient with AML who achieved a CRp was 73.4+ weeks. The median duration of remission for patients with AML who achieved at least a PR (CR + CRP + PR) was 16.2 weeks.

- The median duration of remission for patients with AML who were refractory to the most recent prior therapy who achieved at least a PR (CR + CRP + PR) was 20.0 weeks.

- The survival for the 1 patient with AML who achieved a CRp was 93.6+ weeks. The median survival for patients with AML who achieved at least a PR (CR + CRP + PR) was 39.0 weeks. The median survival for all patients with AML was 21.0 weeks.

The Kaplan-Meier survival curves for CLO-212 are presented below by response group and for all patients.



The bulleted items below address efficacy in patients proceeding to transplant for CLO-212 and CLO-222 combined:

- Twenty patients proceeded to transplant. Of these patients, 8/49 (16%) had ALL and 12/35 (34%) had AML. One of the patients with ALL was not in remission when transplanted, thus this patient is not included as having received clinical benefit from clofarabine.
- Twenty-two of 84 patients benefited from single-agent treatment with clofarabine either through proceeding to transplant or sustaining a durable remission. Of these patients, 10/49 (20%) had ALL (7 who proceeded to transplant and 3 with durable remission) and 12/35 (34%) had AML (all proceeded to transplant).

The management of high-risk (multiply relapsed or refractory patients) pediatric acute leukemia populations involves proceeding to transplant almost immediately after the last cycle of chemotherapy for those patients where a donor is available, without necessarily waiting for full ANC recovery ($\geq 1.0 \times 10^9$/L). This management paradigm is applicable to

patients that are at a high risk of relapse—such as those patients enrolled in CLO-212 and CLO-222—who have relapsed following several prior induction regimens or patients who were refractory to the most recent prior regimen. Investigators participating in these pivotal Phase II studies recommended patients who achieved a PR (or even patients who did not achieve a CR or PR per the IRRP but who had substantial cytoreduction) proceed to transplant without allotting time for complete hematologic recovery or additional cycles of clofarabine. In this regard, the CR/CRp rate would have likely been higher in the Phase II studies if not for this practice pattern. In this patient population, the value of a PR (especially with an M1 marrow without full count recovery) is significant as these patients are often taken directly to transplant and its associated clinical benefit without undergoing additional cycles of clofarabine or allowing time for recovery of normal hematopoiesis.

FINDINGS FROM THE PHASE II STUDIES

There were several key, unexpected findings from these studies.

- The modern-day patients in these studies were considerably more heavily pretreated than what has been reported in the literature for pediatric Phase II studies. The majority of the population studied was refractory (30/49, 61% of patients with ALL; 22/35, 63% of patients with AML) and had been exposed to essentially all combinations of agents with any known activity against pediatric acute leukemias.

- The clinical practice patterns that were current during these studies included taking patients to transplant as soon as patients achieved response or cytoreduction. This approach limited the exposure to clofarabine and may have reduced the OR rate. However, it is understandable that physicians would be more concerned with getting their patients what is essentially one last chance at transplant than whether the patients achieve full count recovery and thus qualify as a "complete response."

These findings may have had a negative impact on the response rate. In spite of these findings, the overall results of the study were strikingly positive in this population. Even patients who did not achieve an IRRP-confirmed CR or CRp received clinical benefit from treatment with clofarabine. We believe that proceeding to transplant and achieving a durable remission (ie, ≥8 weeks) are distinct benefits received by a substantial number of patients as a result of clofarabine treatment. Although not a prospectively defined endpoint, it is striking

that 29/109 patients (27%) in the Phase I study and the 2 pivotal Phase II trials proceeded to transplant or achieved durable remission.

SAFETY

A large number of the adverse effects were already present in many of the patients at baseline. In fact, 98% of the patients in the 2 pivotal Phase II studies had at least 1 concurrent condition at baseline. The most frequent pre-existing conditions included alopecia, tachycardia, fatigue, pyrexia, nausea, anorexia, and vomiting, each of which was present in at least 20% of the patients at baseline. The most common on-study toxicities that were observed with clofarabine, regardless of causality, were gastrointestinal system adverse events (AEs), including vomiting, nausea, and diarrhea; adverse hematologic effects, including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile neutropenia; and infection.

The most commonly reported events of grade 3 or 4 severity, regardless of causality, were febrile neutropenia (grade 3, 54%; grade 4, 4%), nausea (grade 3, 15%; grade 4, 1%), pyrexia (grade 3, 15%; grade 4, 0%), and epistaxis (grade 3, 14%; grade 4, 0%). Most of these events could also have been a result of the patient's underlying disease and are typical of most chemotherapy agents.

Other toxicities of interest include the following:

- Transient elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), typically of <2 weeks duration were observed and generally not considered to be clinically significant. Although less common, there were also elevations in bilirubin, which took from 4 to 32 days to return to baseline or ≤ grade 2. The increases in transaminases and bilirubin could also have been influenced by the use of concomitant medications, eg, voriconazole and cyclosporine.

- Increases in creatinine were observed in some patients. However, the majority of these increases occurred in patients with other concurrent disease processes (eg, sepsis, tumor lysis) or concomitant medications, (eg, amphotericin B, aminoglycoside use, or vancomycin). Duration of elevated creatinine ranged from 1 to 22 days, and appeared to be associated with the duration of the underlying condition.

- Systemic inflammatory response syndrome (SIRS) and capillary leak syndrome were observed in several patients. This disorder has been associated with many oncolytics, including cytarabine, gemcitabine, taxotere, and possibly cladribine. It should also be noted that underlying toxicities from prior therapies, infections, or disease progression may not only cause many of the same symptoms of SIRS/capillary leak syndrome, but may also predispose patients to this condition.

- Based on preclinical data in 1 species and in agreement with the FDA, cardiac function was monitored in these studies. Decline in cardiac function was observed in several patients; however, follow-up echocardiograms (ECHOs) were frequently performed at times when the patients were ill from disease progression, sepsis, or following the development of other substantial medical conditions. Twelve patients with ALL and 10 patients with AML developed treatment-emergent hypotension. These episodes appeared to be related to severe or systemic infections in the vast majority of cases. Patients who had hypotension associated with an infection tended not to experience hypotension during subsequent cycles of treatment.

In conclusion, the safety profile for clofarabine remains as expected in this heavily pre-treated and generally immunocompromised patient population. The observed toxicities are acceptable considering the prognosis of these patients and the lack of other available treatments.[

PHARMACOKINETICS

Clofarabine pharmacokinetics in pediatric patients with leukemia were linear and dose-proportional. Total systemic clearance (CL) and volume of distribution were weight-dependent, while volume of distribution was also dependent on white blood cell (WBC) count. The average CL and volume of distribution at steady-state (Vdss) in patients with ALL was 33 L/h/m^2 and 187 L/m^2, respectively, while the average CL and Vdss in patients with AML was 27 L/h/m^2 and 182 L/m^2, respectively. Half-life was 5 hours in patients with ALL and 6 hours in patients with AML. Renal clearance contributed the largest to CL with ~50-60% excreted in the urine. After controlling for weight, no differences in pharmacokinetics were observed between patients with ALL or AML, between sexes or across ages. Despite a wide range of total doses administered, exposure was consistent across patients, thus underscoring the need to dose based on body surface area (BSA). Clofarabine triphosphate concentrations increased with dose in a nonlinear fashion.

SUMMARY AND CONCLUSIONS

To illustrate the clinical benefit provided by clofarabine, a brief description of a few patients from CLO-212 and CLO-222 is provided. For example, in CLO-212, a 16-year-old male with ALL had failed multiple prior regimens, including both a bone marrow transplant (BMT) and peripheral blood stem cell transplant (PBSCT). Just prior to entering the clofarabine trial he was given single-agent vincristine in an attempt to control his disease. Since he did not respond to vincristine, he was entered into the Phase II study of clofarabine. After 2 cycles of clofarabine this patient was a CR and as of data cut-off, he had received 8 cycles of clofarabine and remained in remission for more than 24+ weeks.

Another patient in CLO-212, a 2-year-old male, had failed to achieve remission with a standard 4-drug induction regimen. He subsequently achieved remission with a regimen of cytoxan, 6-mercaptopurine, and ara-C and underwent a matched unrelated donor (MUD) BMT using high-dose cytoxan and total body irradiation (TBI). After his second remission induction and BMT, he stayed in remission for a period of 17 weeks before relapse was noted. Following relapse, he was entered into the Phase II clofarabine study and achieved a CRp after 1 cycle of treatment. He received 3 cycles of clofarabine and eventually underwent an allogenic BMT. His remission lasted 28.6 weeks with single agent clofarabine followed by BMT, substantially longer than with his most recent previous multi-agent regimen and BMT.

An 11-year-old male patient with M4 AML had failed to respond to cladribine and idarubicin (POG9720) before entering the CLO-222 clofarabine study. He received 1 cycle of clofarabine, which reduced his bone marrow blasts from 52% at study entry to 0%. He went off study with an increasing ANC and no peripheral blasts in order to undergo a cord blood MUD transplant. While this patient was considered a PR by study criteria, he has remained in remission for 57+ weeks following clofarabine and transplant.

In conclusion, there is sufficient evidence to demonstrate the benefit of administering clofarabine to patients with advanced acute leukemia, particularly with its good safety profile. Taking into account the observed response rates, the number of durable remissions,

and the patients who were able to proceed to transplant due to cytoreduction, clofarabine provided benefit to a substantial number of patients.

Despite closure of the pivotal studies, there is continuing demand for access to clofarabine through the Emergency Expanded Access Program (EEAP). Patients from Canada, South America, Europe, Puerto Rico, as well as patients in the US have sought access to clofarabine and many have been treated.

Overall, the benefit of clofarabine far outweighs the risks associated with treatment and the dismal prognosis that faces this population.

FUTURE PLANS

The Children's Oncology Group (COG) is actively designing studies of clofarabine in combination with a variety of other agents in pediatric leukemia patients. These studies will, in a step-wise approach, assist in bringing clofarabine to less heavily pretreated patients and, eventually, to newly diagnosed patients. Clofarabine in combination with cyclophosphamide is being studied at Johns Hopkins Cancer Center in children with acute leukemias.

In addition to the development of clofarabine in pediatric patients, ILEX is pursuing an adult AML registration strategy with the FDA. A teleconference is scheduled in the 4th quarter of 2004 to discuss how to proceed with the adult AML development program. ILEX is currently analyzing data from a study using clofarabine in combination with ara-C in the treatment of adults with hematologic malignancies, and the oral formulation of clofarabine is currently in clinical trial in adults with solid tumors.

1. INTRODUCTION

1.1. Pediatric Leukemia Background

Leukemia is the most common cancer in the pediatric population; acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) are the two most common types of leukemia in pediatric patients. Each year in the United States, approximately 2000 children are diagnosed with ALL, 500 with AML, and <100 with chronic myeloid leukemia (CML).[1] Current therapeutic regimens cure as many as 70% of pediatric patients with ALL and 50% of pediatric patients with AML.[2,3] In newly diagnosed patients with AML, there are several approaches to dose intensification and combination therapy based upon an ara-C backbone are usually employed.[3] In newly diagnosed patients with ALL, treatment is more complex, and—for example—may include alkylating agents, antimetabolites, and anthracyclines.

Unfortunately, the underlying leukemogenic disease process–whether in myeloid or lymphoid clonality–is not permanently eliminated in the 30% of patients with ALL and the 50% of patients with AML who are not cured.[4,5,6] Refractory patients may have responded and achieved remission at some point, but then never again achieve remission, whereas relapsed patients achieve remission but their disease recurs. Collectively, multiply relapsed and refractory patients are known to be highly resistant to therapy and represent an extremely challenging subpopulation of leukemia patients.

Once a pediatric patient relapses, the primary therapeutic alternatives include chemotherapy with or without transplant. For pediatric patients, the timing of relapse is an important prognostic indicator of the type of treatment that should be considered. Relapses are generally classified as early or late. Early relapses occur while on therapy or within 6 months of completing therapy, and late relapses occur more than 6 months off therapy. Relapses can occur in the bone marrow as well as in extramedullary sites, including the central nervous system (CNS) or testes.

In recent years, treatment strategies for pediatric leukemias have increased in intensity and complexity. A consequence of current chemotherapy practices is that the present relapsed

pediatric population has been exposed to more rigorous and intense chemotherapy treatments than patients were 10 to 20 years ago.[7,8,9] Current treatments of cyclic, rotating therapies with combinations of agents with many different mechanisms of action have resulted in relapsed patients who have broad resistance to most of the currently used oncolytics, and who cannot tolerate further chemotherapies due to accumulated organ toxicities, especially cardiovascular, renal, hepatic, and myelosuppressive toxicities. With more intense therapies, accumulated toxicities have become a more difficult clinical issue.[9] Today's relapsing patients are more resistant to subsequent chemotherapy and are thus more challenging and more compromised, often having intercurrent conditions and residual organ toxicity from prior therapies.

Relapse may occur after initial chemotherapy or after a second or third remission. In addition to relapsing after chemotherapy, patients can relapse after transplant. Treatment outcomes appear to be better for patients in first relapse versus patients in second or later relapse.[4,10] In general, pediatric patients in second remission have a higher probability of event-free survival and long-term survival than those treated after subsequent relapses.[4,5,6] In this regard, the patients studied in this submission represent a population with highly resistant disease, who have become refractory to standard agents, and who have a dismal prognosis.

1.2. Management of Pediatric Patients with Relapsed/Refractory Leukemia

The treatment outcomes of pediatric patients who relapse in second or third remission are characterized by a substantially decreased long-term probability for a complete cure.[5] In a study by Buchanan et al of children with ALL, 258/297 patients achieved a second complete hematologic remission; however, only 23 (7.7%) remained continuously leukemia free for 7 or more years after chemotherapy or BMT.[4,11] Most second relapses in the Buchanan study occurred within the first year after achieving second remission, with a median duration of remission of 7 months and median survival of 12 months. It is probable that hematologic relapse during initial chemotherapy or shortly after its completion signifies drug-resistant leukemia in most cases.[11]

Earlier treatments were predominantly cyclic combinations of chemotherapy and irradiation, but did not involve transplant.[2] Today's treatment regimens for relapsed pediatric ALL[12,13,14,15,16,17,18] and relapsed pediatric AML[10,19,20] incorporate the early use of myeloablative transplant as a major treatment component. For example studies have been conducted using a variety of different combinations of chemotherapy agents, including idarubicin plus fludarabine and cytarabine as treatment for refractory or recurrent AML.[21] Treatments for recurrent ALL in children have included combination regimens such as vincristine in combination with cytarabine, methotrexate, and L-asparaginase; vincristine in combination with cytarabine, methotrexate, teniposide, L-asparaginase, and 6-mercaptopurine, and ifosfamide in combination with methotrexate, 6-thioguanine, vindesine, and daunorubicin.[4] These treatment regimens have evolved from single-arm clinical studies in the absence of randomized, controlled clinical trials in these populations.

Patients who proceed to transplant have a better probability of obtaining a durable long-term, event-free survival compared with those multiply relapsed patients who are treated with chemotherapy alone. Patients who proceed to HSCT early in the course of their leukemia and with a low tumor burden were found to have improved survival.[22] Therefore, a major goal for patients with multiply relapsed leukemia is to reduce the tumor burden and to proceed to transplant as quickly as possible.

Transplant is an established therapeutic intervention for pediatric patients with relapsed or primary refractory ALL or AML, especially for patients in second or later remission. Since positive transplant outcomes are clearly related to disease burden at the time of transplant, reduction of tumor burden prior to transplant is a primary goal.[22]

1.3. Conclusions

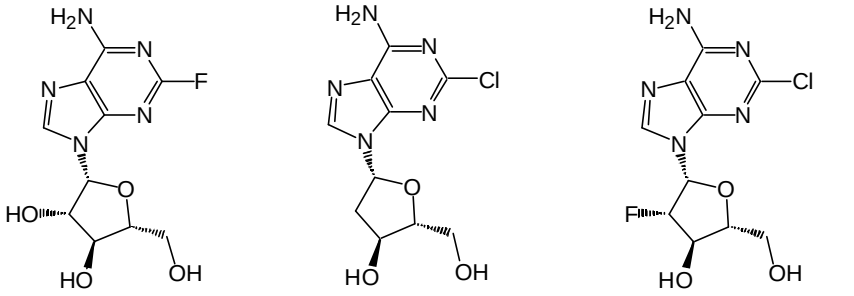
While great strides have been made in the treatment of children newly diagnosed with leukemia, successful treatment of relapsed and refractory pediatric leukemias remains an unmet medical need. The number of children with relapsed or refractory leukemia is higher than the incidence of most pediatric malignancies. Approximately 20% to 30% of patients with ALL and an even higher percentage (50%) of patients with AML relapse to currently

available treatments. These patients are more resistant to remission reinduction attempts and have accumulated organ toxicities, especially cardiovascular, renal, and hepatic. They also have diminished marrow reserves and are prone to prolonged myelosuppression. Clearly this population is in need of new therapeutic options for another remission induction attempt with a drug to which the patient is not cross resistant and does not have toxicities similar to those already experienced. Clofarabine satisfied this unmet medical need.

1.4. Clofarabine Background Information

Clofarabine is a second generation purine nucleoside antimetabolite. Originally synthesized at the Southern Research Institute, clofarabine was designed as a hybrid molecule to overcome the limitations and incorporate the best qualities of both fludarabine (Fludara®) and cladribine (Leustatin®). It is differentiated from other purine nucleoside analogues by incorporating 2 halogen atoms (fluorine and chlorine) within its chemical structure. See Figure 1 below.

Figure 1: Structure of Deoxyadenosine Analogues and Clofarabine



Fludarabine
(2-fluoro Ara A)

2-CdA
(2-chloro-2'-deoxyadenosine)

Clofarabine
(2-chloro-2'-fluoro Ara A)

Clofarabine is a nucleoside pro-drug that must be metabolized to its monophosphate conjugate by deoxycytidine kinase followed by phosphorylation to triphosphate within tumor cells before activity occurs. Compared to other purine nucleoside analogues, it has greater affinity for the activating phosphorylating enzyme deoxycytidine kinase and other kinases. The mechanism of action of clofarabine is discussed in Section 2.1.

Clofarabine has demonstrated potent cytotoxic activity in a wide range of cell lines, including leukemia, non-small cell lung, colon, melanoma, ovarian, renal, prostate, and breast cancer lines.[23,24] Therapeutic activity has also been shown in murine tumor models (P388 leukemia, colon 36, and mammary 16/c).[25] Curative activity was shown in solid tumor models including early and advanced stages of HT-29 and colon 36 xenograft tumor models.[25,26] Clofarabine is active against a wide range of in vivo and in vitro human tumor models, including solid tumor and hematologic tumor types.[25,27,28,29,30,31,32,33,34,35,36,37,38,39,40]

1.5. Overview of the Clofarabine Clinical Development Program

In March 2002, ILEX assumed responsibility for the M. D. Anderson Cancer Center (MDACC) Investigational New Drug (IND) No. 43,275. Clofarabine was granted Orphan Drug Designation for adult and pediatric ALL on 07 February 2002 and Orphan Drug Designation for adult and pediatric AML on 14 March 2002. The ILEX pre-IND meeting was held on 30 August 2001 and the ILEX IND No. 63,641 was opened on 07 December 2001. The MDACC studies were transferred to the ILEX IND on 11 April 2002.

An End-of-Phase II meeting was held with the FDA on 29 April 2002. ILEX requested Fast Track Designation on 08 May 2003, which was approved by the FDA on 08 July 2003. A preNDA package was submitted to the FDA on 15 July 2003. On 13 August 2003, ILEX and the FDA had a preNDA teleconference where the following key points were addressed:

- The study designs for CLO-212 and CLO-222 were determined to be acceptable as pivotal studies.
- The proportion of responding patients who have a successful transplant was determined to be an important issue.
- The COG Response Criteria could be acceptable after review by the FDA.
- No prespecified minimum OR rate was agreed upon with the FDA for establishing efficacy. FDA stated that identification of a clinically meaningful response rate would be a review issue.
- CR/CRp/PR can be considered a clinical benefit, depending on response duration, survival, toxicity, and results achievable with other therapy.

- For transplant patients, clinical benefit depends upon the success of transplant after treatment with clofarabine.
- The rolling NDA submission was determined to be acceptable.
- The pharmacokinetic/pharmacodynamic section of the analysis plan was determined to be acceptable.
- ILEX's study design and the endpoints for the ALL study were accepted by the FDA, who determined this approach would be acceptable as the model for the AML study.
- FDA agreed to ILEX's proposal to increase enrollment on CLO-212 from 40 to 60 patients.

On 14 July 2004, the FDA granted ILEX 6 months additional exclusivity for clofarabine.

A total of 362 patients have been treated with clofarabine as of the data cutoff, of which 113 were pediatric patients. Table 1 provides a chronology of the clofarabine studies including the study sponsor, ongoing emergency expanded access patients, and the population and indication.

Table 1: Chronology of Clinical Studies Conducted with Clofarabine

Protocol	Sponsor	Date Initiated	Patient Population/ # Patients Treated	Phase of Study	Disease Description
DM93-036	MDACC	Feb 1999	Adult 51 patients (2 were pediatric)	Phase I	Solid and Hematologic Malignancies
DM99-225	MDACC	Sep 1999	Adult 11 patients	Phase II	CLL (Refractory to Fludarabine and Alkylator Therapy)
ID99-383	MDACC	Aug 2000	Pediatric 25 patients	Phase I	Hematologic Malignancies
ID00-038	MDACC	May 2001	Adult 64 patients	Phase II	Acute Leukemia and Myelodysplastic Syndrome Refractory to Therapy or in Relapse
CLO-221	ILEX	Nov 2001	Adult 40 patients (1 was pediatric)	Phase II	AML
CLO-212[a]	ILEX	Apr 2002	Pediatric 49 patients	Phase II	ALL
CLO-222[a]	ILEX	Jan 2002	Pediatric 35 patients	Phase II	AML
CLO-151[a]	ILEX	May 2002	Adult 26 patients	Phase II	Solid Tumors
CLO-141	ILEX	June 2002	Adult 32 patients (1 was pediatric)	Phase II	Clofarabine in Combination with ara-C in AML or ALL; with High-Risk MDS; or with CML Blast Phase as Front Line Therapy or in First Salvage
Expanded Access[a,b]	ILEX	Jan 2002	Adult/Pediatric 29 patients (23 were pediatric)	--	AML and ALL

[a] Ongoing
[b] As of 01 October 2004

1.6. Proposed Indication of Clofarabine

Clofarabine is indicated for the treatment of pediatric patients 1 to 21 years old with refractory or relapsed acute leukemias.

1.7. Proposed Clofarabine Dosing Regimen and Duration of Treatment

Clofarabine should be diluted per the instructions on the label with 5% dextrose injection, United States Pharmacopeia (USP) or European Pharmacopaeia (EP) or 0.9% sodium chloride injection, USP or EP prior to IV infusion. The recommended pediatric dose and schedule for acute leukemias is 52 mg/m^2/day administered by IVI over 1 to 2 hours daily for 5 consecutive days. Treatment cycles are repeated every 2 to 6 weeks following recovery or return to baseline organ function. The dosage is based on the patient's BSA, calculated using the actual height and weight before the start of each cycle. To prevent drug incompatibilities, no other medications should be administered through the same intravenous (IV) line. Clofarabine has been used in adults at a dose of 40 mg/m^2/day for Induction followed by 30 mg/m^2/day for Consolidation.

2. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

2.1. Mechanism of Action

Clofarabine (2-chloro-2'-arabino-fluoro-2'-deoxyadenosine) is a halogenated-deoxyadenosine analogue. Based upon its mechanism of action as an inhibitor of both ribonucleotide reductase and DNA polymerase α and ε, clofarabine is a member of a class of nucleoside analogues that includes gemcitabine, fludarabine, and cladribine.[31] However, clofarabine differs from other nucleoside analogues in several ways:

- The efficiency (Vmax/Km) of phosphorylation of clofarabine by deoxycytidine kinase (dCK) is equal to or greater than that of its natural substrate deoxycytidine (dCyd), and significantly greater than that of cladribine (~3-4 times greater) and fludarabine (~25 times greater).[29,41]

- Clofarabine has higher retention and greater accumulation in the lymphocytes of CLL patients than does cladribine.

- Clofarabine and cladribine produce apoptosis through a direct and indirect pathway, whereas fludarabine produces apoptosis only through an indirect pathway.

- The inhibitory potency of clofarabine triphosphate on ribonucleotide reductase was similar to that of cladribine triphosphate, 10 times greater than fludarabine triphosphate,[31] and 100 times greater than gemcitabine triphosphate.[41]

- The inhibition of DNA chain elongation by polymerase α by clofarabine triphosphate was similar to that of fludarabine triphosphate but greater than that of cladribine triphosphate.

- Peak concentration of clofarabine triphosphate in CLL and AML cells were 3 to 4 fold higher than for cladribine triphosphate.[29]

- Clofarabine triphosphate, the active metabolite, has longer retention times in blasts of patients with acute leukemias than fludarabine and cladribine triphosphates.[42,43,44]

- The intracellular half life ($t_{1/2}$) was longer for clofarabine triphosphate (7.3 hours) than for cladribine triphosphate (4.3 hours).

- The 48-hour concentration of clofarabine triphosphate was more than 2-fold greater than that measured for cladribine.

- Clofarabine possesses biochemical and pharmacokinetic advantages over fludarabine and cladribine. At the end of infusion at doses of 40 mg/m^2/day for adults and 52 mg/m^2/day for children, a median plasma level of 1-2 µM clofarabine is achieved.[45]

Clofarabine was rationally designed to be more resistant to deamination by the enzyme adenosine deaminase, to be more stable to degradation by gastric acid, and to decrease its susceptibility to phosphorolytic cleavage by the bacterial enzyme purine nucleoside phosphorylase in the gastrointestinal tract.[27,46]

Clofarabine is a slightly lipophilic prodrug that gains entry into cells by facilitative and active nucleoside transporter mechanisms, and by passive diffusion across lipid membranes. Thus, clofarabine administration would be expected to result in wide distribution of drug into tumor and normal tissue. Tissue distribution studies have been conducted with clofarabine in mice and rats.[47,48] Except for tissues with special barriers, eg, eye, brain, and testes, which had low drug concentrations, clofarabine distribution was fairly widespread with the highest concentrations occurring in the excretory/metabolic organs and gastrointestinal tract (ie, kidney, small intestine, liver, and large intestine). The low concentration of clofarabine in brain tissue would suggest that the neural toxicity seen clinically with fludarabine might not occur with clofarabine.

Once inside the cell, clofarabine is step-wise phosphorylated to its 5'-mono-, di-, and tri-phosphorylated form for activity. Deoxycytidine kinase (dCK), a key cytosolic enzyme in the DNA synthesis salvage pathway, is responsible for the phosphorylation of clofarabine to its mono-phosphate form. Studies with purified dCK from human Molt-4 lymphoblasts and with purified recombinant human dCK have shown that the efficiency (Vmax/Km) of clofarabine phosphorylation was equal to or greater than that of the natural substrate, deoxycytidine, and significantly greater than that of cladribine and fludarabine.[29] Both clofarabine monophosphate and triphosphate accumulate at higher levels than clofarabine diphosphate.

Based upon accumulation of clofarabine monophosphate and clofarabine triphosphate in cells, the rate-limiting step in the synthesis of clofarabine triphosphate is the conversion of

clofarabine monophosphate to clofarabine diphosphate by a purine nucleotide monophosphate kinase.[49] The monophosphate metabolite within cells may act as a reservoir for the formation of the triphosphate metabolite. This is in contrast to fludarabine where dCK is the rate-limiting enzyme in its activation.[49] In incubation studies with blood from patients with CLL or AML, clofarabine showed higher peak (~3-4 fold) and 48-hour (~2 fold) concentrations compared to that of cladribine.[29]

The anticancer activity of clofarabine is believed to be due to 3 mechanisms:

- DNA polymerase α and ε inhibition resulting in termination of DNA elongation and/or DNA synthesis repair,[31] by DNA-incorporated clofarabine
- Ribonucleotide reductase inhibition by clofarabine triphosphate with reduction of dNTP pools,[31]
- Induction of apoptosis through direct and indirect actions on mitochondria by releasing cytochrome C and other proapoptotic factors.[32]

DNA polymerase nuclear enzymes are responsible for the incorporation of dATP into DNA. Clofarabine triphosphate is a potent competitive inhibitor (K_i of 1 μM) of DNA polymerase α and competes with dATP for incorporation into DNA. The inhibitory potency of clofarabine on polymerase α is similar to that of fludarabine, but significantly greater than that of cladribine. In addition, DNA elongation and/or repair are impaired by the incorporation of clofarabine monophosphate into the DNA through chain termination and strand breakage.

Clofarabine triphosphate is a particularly potent inhibitor of ribonucleotide reductase (IC_{50}, 65 nM) and depletes the intracellular dNTP pool (ie, dATP, dCTP, and dGTP, but not dTTP). The inhibitory potency of clofarabine triphosphate on ribonucleotide reductase is similar to that of cladribine, but approximately 10 fold greater than fludarabine. The marked reduction in dCTP appears to be sufficient to limit DNA synthesis. In addition, the marked reduction in dATP creates a favorable environment for clofarabine triphosphate to compete with dATP for incorporation into DNA. When the ratio of clofarabine triphosphate to dATP is >1, clofarabine monophosphate is preferentially inserted into the end of the DNA chain resulting in termination of chain elongation. A ratio of clofarabine triphosphate to dATP <1 results in insertion of clofarabine monophosphate into the middle of the DNA structure and inhibits

DNA repair. These two actions of clofarabine on DNA synthesis and induction of apoptosis have been cited as mechanisms to explain clofarabine's anticancer activity in both rapidly growing and quiescent tumors.[27] This damage to DNA produces strand breaks and initiates a chain of events that results in release of cytochrome C from the mitochondria and activation of cellular suicide (apoptosis).

Clofarabine has also been shown to act directly on mitochondria by altering the transmembrane potential, which results in release of cytochrome C and apoptotic-inducing factor (AIF). Binding of cytochrome C, apoptosis protease activating factor 1 (Apaf-1), and procaspase 9 into the cytosol initiates the apoptosis cascade.[32] Thus, clofarabine induces apoptosis in cells by two separate pathways (ie, a direct action on the mitochondria and an indirect pathway via DNA damage). Fludarabine apparently induces apoptosis only through an indirect action on the mitochodria.[32]

2.2. Antitumor Activity

As expected from its potent inhibition of DNA synthesis, clofarabine demonstrated strong in vitro growth inhibitory and cytotoxic activity (IC_{50} values ranged from 0.028 to 0.29 µM) in a wide variety of leukemia and solid tumor cell lines.[25] When tested in the panel of 60 human tumor cell lines of the National Cancer Institute's Developmental Therapeutics Program, clofarabine demonstrated potent growth inhibitory activity (GI_{50} values from <0.0001 to 0.45 µM) for 35 of the tumor cell lines. The tumor cell types sensitive to clofarabine included non-small cell lung (6 cell lines), colon (6 cell lines), central nervous system (3 cell lines), melanoma (4 cell lines), ovarian (4 cell lines), renal (6 cell lines), prostate (2 cell lines), and breast (4 cell lines).

Clofarabine administered intraperitoneally (IP) exhibited significant activity against a wide variety of human tumor xenografts implanted subcutaneously (SC) in athymic nude or severe combined immunodeficient (SCID) mice.[25] Moderate to excellent sensitivity to tumor growth delays were seen in all 8 human colon tumors, 3 of 4 human renal tumors, all 4 non-small cell lung tumors, and all 3 prostate tumors. This spectrum of widespread anticancer activity has been confirmed by other investigators in human tumor xenograft models in

mice.[33] The anticancer activity of clofarabine was dose and schedule dependent, with greater antitumor activity associated with more frequent administration. The optimum dosing schedule for all the tumor types tested in mice consisted of 3 injections separated by 4 hours every day for 8 consecutive days. These data suggest that anticancer activity is increased when clofarabine is administered as multiple daily doses on consecutive days for prolonged periods of time.

Similarly, increased toxicity was observed in a 7-daily dose mouse study when the daily dose was administered as 2 separate IP injections.[50] The reason for the increased activity associated with more frequent administration is not known but may be related to one or more possible mechanisms, the most likely being the need to maintain a constant level of DNA synthesis inhibition through sustained triphosphate metabolite concentrations.

Results from the in vitro mechanism of action studies in lymphoblastoid cells show that there is an accumulation of clofarabine monophosphate; this accumulation can act as a reservoir for a continued source of clofarabine triphosphate. Another possible explanation is clofarabine-induced activation of dCK occurring shortly after exposure. For example, short-term pretreatment (ie, 1-5 hours) with clofarabine has been shown to increase the activity of dCK in HL60 cells,[51] and increased the formation of the mono-, di-, and triphosphates of ara-C in K562 cells.[45] Thus, the initial dose of clofarabine could induce higher dCK concentrations that would result in increased activation of clofarabine upon administration of a subsequent daily dose.

Greater anticancer activity has been observed in human tumor xenograft mouse models when similar doses of clofarabine were administered orally (PO) as opposed to IP. The increased anticancer activity following PO administration is particularly interesting since pharmacokinetic studies have indicated that orally administered clofarabine is approximately 57 to 81% bioavailable in mice.[52] Similar to the findings following IP administration, anticancer activity is increased when clofarabine is administered PO daily for 8 to 53 consecutive days. The results obtained following PO administration are consistent with the hypothesis that the anticancer activity of clofarabine is primarily associated with total

systemic exposure (AUC) or time above a threshold rather than peak plasma concentrations (Cmax).

2.3. Toxicology

Based upon its mechanism of action, which includes decreased DNA synthesis and repair and the induction of apoptosis through a direct and indirect action on the mitochondria, clofarabine would be expected to have an adverse effect on the rapidly proliferating tissues (eg, bone marrow, gastrointestinal tract, testes, lymph tissue, etc), induce clastogenic effects in genotoxicity tests, and show evidence of teratogenicity in developmental toxicity tests. As expected, clofarabine induced positive findings in the in vitro chromosomal aberration test, in vivo micronucleus assay, and in the rat and rabbit developmental toxicity tests. Clofarabine also induced the expected adverse effects on the lymphoid tissues, bone marrow, gastrointestinal tract, and testes of mice, rats, and dogs. Interestingly, the MTD, DLT, and sensitivity of the bone marrow, gastrointestinal tract, lymphoid tissue, and testes to clofarabine-induced toxicity varied among mice, rats, and dogs. Based upon their respective MTD values (on a daily × 5 schedule), the dog was the most sensitive species, followed by the rat and mouse. See Table 2.

Table 2: Preclinical Dose-Limiting Toxicities

	MTD		DLT
	mg/kg/day	**mg/m^2/day**	
Mouse[a]	75	225	Gastrointestinal tract
Rat Single-Cycle Chronic[b]	 25 12.5	 150 75	 Heart
Dog[b]	0.75	15	Gastrointestinal tract

[a] 7-day acute study
[b] 6-month chronic toxicity study

The dog was uniquely sensitive to clofarabine-induced gastrointestinal toxicity and deaths from gastrointestinal toxicity were observed following doses of 1.5 mg/kg/day

(30 mg/m^2/day). Gastrointestinal toxicity was also the DLT in mice, but was seen at much higher doses compared to dogs. Rats, on the other hand, were relatively resistant to gastrointestinal tract toxicity. The relative lack of toxicity in the rat was apparently not related to differences in tissue distribution, since intestinal tissue was one of the organs with high clofarabine or clofarabine-equivalent concentrations in the mass balance study in rats.

The reason for this species difference is not known. However, the experience gained from toxicity studies with other antimetabolite anticancer agents may provide a clue. For example, the toxicity of cladribine and fludarabine in mice and dogs underestimated the bone marrow toxicity and DLT observed in their initial clinical trials.[53,54,55] The reason for this underestimation was attributed to a much higher dCK concentration in the bone marrow of humans compared to mice and dogs. High dCK tissue concentrations are normally seen in the lymphoid tissues of most species, but its concentration in other tissues, although biologically significant, shows considerable species specificity.[56,57,58]

Histopathological evidence of cellular depletion in the bone marrow was seen in mice, rats, and dogs at doses approximating their respective MTD values. Decreases in circulating white blood cells, particularly lymphocytes, were generally seen in animals at doses much lower than those showing histopathologic effects on bone marrow. The decrease in circulating white blood cells and a cellular depletion in lymphoid tissues (eg, spleen and thymus) was particularly prominent in oral studies and in studies employing prolonged IV infusion (~1 hour). One explanation for the increased sensitivity of lymphoid tissue and circulating white blood cells with prolonged clofarabine exposure may be related to a direct toxic effect on lymphocytes and possibly other white blood cells. Clofarabine has been shown in vitro and in vivo to have a potent cytotoxic effect on nondividing lymphocytes.[27] Thus, the decrease in circulating white blood cells seen in some of the early toxicity studies, an effect attributed to bone marrow toxicity, may have been instead related to a direct cytotoxic effect on the circulating cells.

Unlike mice and dogs, clofarabine administration in rats induced adverse histopathological effects on the heart in acute and chronic toxicity studies, and in the liver in the chronic

toxicity study. The adverse effects on the heart were observed in the 5-daily dose studies at doses of 50 mg/kg/day (300 mg/m^2/day) and in the chronic toxicity study with 6 cycles of 5-daily doses repeated every 28 days at doses of 25 mg/kg/day (150 mg/m^2/day). The cardiotoxicity became particularly evident after 3 months of study. The minimal cardiac toxicity seen at lower doses in these studies suggests that there is a threshold for adverse effects on the heart. The histopathologic lesion in the heart is confined to tissues on the left side of the heart, suggesting a possible interference with mitochondrial function and energy production.

Interestingly, nonlinear plasma pharmacokinetics have been repeatedly demonstrated at doses between 25 mg/kg and 50 mg/kg (150 mg/m^2/day) in the rat and this nonlinearity may play a role in the observed cardiotoxicity. Evidence is also accumulating, suggesting that cardiotoxicity is related primarily to high Cmax as opposed to AUC, as a reduction in cardiotoxicity was seen with oral dosing (even after factoring in a reduction in bioavailability) and when drug was administered as a 1-hour infusion as opposed to bolus administration. At the present time, it is difficult to determine whether the cardiotoxicity seen in rats is species specific. For example, the lack of cardiotoxicity in the dog may be related to an inability to achieve equivalent exposure in dogs relative to rats because of the gastrointestinal toxicity seen at low doses in dogs. On the other hand, cardiotoxicity was not a significant finding in mice, even though they were administered higher doses than the rat and have higher heart rates, which should make them more prone to cardiotoxicity, especially if the cardiotoxicity is associated with diminished energy production.

Overall, it should be noted that the cardiac toxicity in rats was observed at doses of clofarabine (≥150 mg/m^2/day) that are substantially higher than the dose being used in the clinical trials in pediatric leukemia, ie, 52 mg/m^2/day. In addition, since clofarabine was administered as a bolus over 1 to 2 minutes in the rat studies as opposed to a 2-hour infusion in the clinical trials, the clofarabine Cmax plasma levels in rats was at least 20-fold higher than in patients.

Significant histopathological evidence of hepatotoxicity was also observed in the 6-month chronic toxicity study in rats, particularly at the 25 mg/kg/day (150 mg/m^2/day) dose level. Single cell necrosis, which is considered a hallmark of cellular apoptosis, was a particularly prominent histopathologic feature. The histopathologic changes were also suggestive of cyclic liver toxicity and recovery associated with each treatment cycle. Since apoptosis resulting from a direct action of clofarabine on the mitochondria and from an indirect effect resulting from DNA damage is considered a mechanism of its anticancer activity, the adverse effect of clofarabine on the liver is likely associated with an extension of its pharmacological anticancer activity.

Overall, the toxicity studies conducted in animals are considered to have provided a good indication of potential target organs of toxicity. However, prediction of the likely DLT, MTD, and most prominent target organs of toxicity from one species to the next is difficult for the variety of reasons discussed above. Principally, those reasons include possible species and tissue differences that are associated with the abundance and tissue distribution of nucleoside transporter systems important for transport of clofarabine into cells, and species differences in tissue dCK concentrations. The multiple mechanisms of action also make such predictions difficult.

3. DOSE RATIONALE

A Phase I pediatric study (ID99-383) provided the foundation for dose selection in the 2 controlled pediatric clinical studies that ILEX conducted: CLO-212 in ALL and CLO-222 in AML.

3.1. Design of Phase I Dose-Escalation Study

ID99-383 was a Phase I, open-label, non-randomized, dose-escalation study in pediatric patients with hematologic malignancies (ALL and AML) who had failed standard therapy or for whom no such therapy existed. Doses were escalated from 11.25 mg/m^2/day to 70 mg/m^2/day.

3.2. Clofarabine Administration Schedules

In ID99-383, clofarabine was administered by intravenous infusion (IVI) daily for 5 consecutive days. Treatment was repeated every 2 to 6 weeks, up to 12 cycles maximum. Table 3 summarizes the extent of exposure to clofarabine by the number of cycles of treatment and dose cohort for all patients. All patients received at least 1 cycle of clofarabine at each of the doses evaluated with an overall range of 1 to 8 cycles. The doses evaluated were 11.25, 30, 40, 52, or 70 mg/m^2/day. More than half of the patients received 52 mg/m^2/day, the dose that was selected for the ILEX Phase II pivotal trials, CLO-212 and CLO-222.

Table 3: ID99-383 Extent of Exposure to Study Drug by Number of Cycles of Treatment and Dose Cohort

Variable		Dose Cohort Clofarabine (mg/m²/daily)					
		11.25 mg/m²/d N=1	30 mg/m²/d N=3	40 mg/m²/d N=6	52 mg/m²/d N=13	70 mg/m²/d N=2	Overall N=25
Cycles of Treatment	Mean	2.0	2.3	2.0	2.5	2.0	2.3
	Median	2.0	2.0	2.0	2.0	2.0	2.0
	Std	.	0.5	0.8	1.7	1.4	1.3
	Min	2.0	2.0	1.0	1.0	1.0	1.0
	Max	2.0	3.0	3.0	8.0	3.0	8.0

3.3. Baseline Demographic Characteristics in the Phase I Dose-Escalation Study

Table 4 summarizes the demographic characteristics of the 25 patients in ID99-383 by dose cohort. The majority of patients were male (15/25 [60%]). Most patients were either Caucasian (13/25 [52%]) or Hispanic (9/25 [36%]). The median age for the 25 patients was 12 years, with a range of 1 to 19 years.

Table 4: ID99-383 Demographics at Enrollment

Variable		Dose Cohort Clofarabine (mg/m²/daily)					
		11.25 mg/m²/d N=1	**30 mg/m²/d N=3**	**40 mg/m²/d N=6**	**52 mg/m²/d N=13**	**70 mg/m²/d N=2**	**Overall N=25**
Age	Mean	12.00	7.33	11.50	9.92	17.00	10.64
	Median	12.00	7.00	12.00	12.00	17.00	12.00
	Std	.	5.51	5.58	5.33	0.00	5.34
	Min	12.00	2.00	2.00	1.00	17.00	1.00
	Max	12.00	13.00	19.00	18.00	17.00	19.00
Sex							
Male	n	1	1	5	7	1	15
	%	100.00	33.33	83.33	53.85	50.00	60.00
Female	n	.	2	1	6	1	10
	%	.	66.67	16.67	46.15	50.00	40.00
Origin							
Caucasian	n	.	.	3	9	1	13
	%	.	.	50.00	69.23	50.00	52.00
Hispanic	n	1	2	2	3	1	9
	%	100.00	66.67	33.33	23.08	50.00	36.00
Black	n	.	.	.	1	.	1
	%	.	.	.	7.69	.	4.00
Asian	n	.	.	1	.	.	1
	%	.	.	16.67	.	.	4.00
Other	n	.	1	.	.	.	1
	%	.	33.33	.	.	.	4.00

3.4. Efficacy Results - Phase I Dose-Escalation Study

Disease response, which was not a primary objective of ID99-383, was to be assessed by bone marrow aspirate before the start of each cycle. Patients who did not achieve some degree of response after 2 cycles were considered to have progressive disease. All but 1 patient were assessed by the investigator for disease response.

The investigators in ID99-383 used different response criteria to assess patients during the study; however, ILEX sponsored an IRRP to conduct a retrospective analysis of all the complete responders according to the criteria that would be used in the pivotal Phase II

studies. Provided below are the definitions and investigators' standard response criteria that were used to assess pediatric leukemia patients at the time this study was conducted.

- **Complete remission (CR):** For leukemia, a rating of 1 in all categories (M1, H1, P1, S1) (see the disease response criteria below). The duration of CR lasts from the first day that the CR was attained until the last day of CR.
- **Partial remission (PR):** For leukemia, a rating of 2 or more in 1 or more categories, but no rating of 3 in any category.
- **Improvement (I):** Improvement of M, H, and/or P to a rating of 1 or 2 with 1 or more categories remaining at a rating of 3.
- **Stable disease (SD):** For leukemia, no changes in any category.
- **Progressive disease (PD):** For leukemia, deterioration from an initial disease status of 1 or 2.

ID99-383 Investigators' Disease Response Criteria

	Rating		
Category	**1**	**2**	**3**
Bone Marrow			
Blasts - %	0 - 5	5 – 25	>25
Hemogram			
Hg g/dL	<2 yr = 10	≥7	<7
Hg g/dL	>2 yr = 11	≥7	<7
Neut. Gran/µL	>1500	≥500 – 1500	<500
Blasts %	0	≤5	>5
Platelets/µL	>100,000	25,000 - ≤100,000	<25,000
Physical Findings			
Liver	Normal for age	≤To Umbilicus	Below Umbilicus
Spleen	Normal for age	Abnormal	Grossly Visible
Other	Normal for age	Definite	Marked
Symptoms/Performance			
Symptoms	Asymptomatic	Moderately Symptomatic	Marked Symptomatic
Performance	Normal Activity	<50% Time in Bed	≥50% Time in Bed

Table 5 summarizes the best objective responses as determined by the investigator to refer to each patient's best response to treatment with clofarabine. These data are presented for all other patients in the Phase I dose-escalation study using the criteria listed above. Of the

25 patients, the investigators determined that 5/25 (20%) achieved a CR, 3/25 (12%) achieved a PR, 7/25 (28%) experienced hematologic improvement, and 4/25 (16%) had stable disease.

Table 5: ID99-383 Investigators' Summary of Best Objective Response

	Dose Cohort of Clofarabine (mg/m²/daily)											
	11.25 mg/m²/d N=1		30 mg/m²/d N=3		40 mg/m²/d N=6		52 mg/m²/d N=13		70 mg/m²/d N=2		Overall N=25	
Response Category	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Complete Remission	.	.	1 (ALL)	33.3	2 (ALL)	33.3	1 (AML)	7.7	1 (ALL)	50.0	5	20.0
Partial Remission	.	.	.	.	2 (AML)	33.3	1 (ALL)	7.7	.	.	3	12.0
Improvement	.	.	.	.	.	.	6 (5 ALL) (1 AML)	46.2	1 (ALL)	50.0	7	28.0
Stable Disease	1 (ALL)	100.0	2 (1 ALL) (1 AML)	66.7	.	.	1 (ALL)	7.7	.	.	4	16.0
Progressive Disease	.	.	.	.	2 (1 ALL) (1 AML)	33.3	3 (2 ALL) (1 AML)	23.1	.	.	5	20.0
Not Evaluable	.	.	.	.	.	.	1 (AML)	7.7	.	.	1	4.0

Total of 17 patients with ALL and 8 patients with AML

ILEX requested an IRRP review the responses of the patients who were assessed as CRs by the investigators in this study to determine what their responses would be under the criteria that were being used in the 2 pivotal Phase II studies. This review determined that of the 5 patients assessed as CRs by the investigators, 2 would still be CRs, 1 would be a CRp, and 2 would be PRs according to the Phase II criteria.

3.5. Safety Results - Phase I Dose-Escalation Study

Overall, the most frequently reported (>20% of the patients) drug-related AEs included vomiting not otherwise specified (NOS), nausea, pruritus NOS, diarrhea NOS, and mucosal inflammation NOS. Drug-related grade 3 or 4 AEs included nausea, vomiting NOS, diarrhea NOS, febrile neutropenia, bone marrow depression NOS, convulsions NOS, dyspnea NOS,

feeling abnormal, headache NOS, Herpes zoster, hyperbilirubinemia, increased ALT and AST, maculopapular rash, post procedural hemorrhage, and skin disorder NOS; none of which were reported by more than 10% of the patients overall. The most frequently reported drug-related SAEs were nausea and vomiting. One patient with ALL discontinued due to an AE of grade 4 hyperbilirubinemia that was serious in nature and drug related. Five patients died within 30 days of the last dose of clofarabine due to progressive disease or AEs secondary to the patients' disease.

Although infections were prevalent in the study, only 1 was considered to be drug related. The most frequently reported infections (≥10%) were abscesses, cellulitis, colitis pseudomembranous, Herpes simplex, implant infections, pneumonia, and sepsis NOS, septicemia, or septic shock.

Two patients treated with 70 mg/m^2/day experienced a DLT: grade 4 hyperbilirubinemia of >30 days duration that resulted in discontinuation from the study in 1 patient and grade 3 maculopapular rash that resulted in a dose reduction from 70 mg/m^2/day to 52 mg/m^2/day in 1 patient. One patient's doses were reduced from 52 to 40 mg/m^2/day to 30 mg/m^2/day and delayed for 2 and 3.5 weeks, respectively, due to drug-related grade 3 and 4 neutropenia and grade 3 and 4 thrombocytopenia.

Infusion times were increased from 1 hour to 2 hours or up to 3 hours if needed for 6 patients (1 at 70 mg/m^2/day, 4 at 52 mg/m^2/day, and 1 at 40 mg/m^2/day) due to drug-related AEs. Two patients in the 52 mg/m^2/day dose cohort received clofarabine administered over more than 1 hour because of an amendment change reflecting infusion-related AEs (eg, anxiety) that occurred during the study.

Each of the 5 patients who died within 30 days of the last dose of clofarabine died due to progressive disease or AEs secondary to the patients' disease.

Overall, pediatric patients with acute leukemias tolerated treatment with clofarabine with drug-related adverse effects that were mainly secondary to the known activity of clofarabine. According to the investigator, the DLTs observed in this study were grade 4

hyperbilirubinemia and grade 3 maculopapular rash observed in 1 patient each in the 70 mg/m^2/day group and the MTD was determined to be 52 mg/m^2/day.

3.6. Pharmacology and Dose Rationale

Plasma clofarabine concentrations increased with increasing dose. Maximal concentrations were observed at the end of infusion and remained quantifiable 24 hours after the start of the infusion (see section 4 for more detailed description of clofarabine pharmacokinetics). Intracellular clofarabine triphosphate concentrations were correlated with plasma clofarabine concentrations but were many-fold higher on a per mL basis. Intracellular clofarabine triphosphate concentrations increased with increasing dose, were highest at the end of infusion, and remained quantifiable 24 hours after the start of infusion.

Further, DNA synthesis inhibition was studied in 4 patients at doses of 11.25, 15, 40, and 52 mg/m^2/day. Generally, DNA synthesis was inhibited in leukemic cells at the end of infusion, but had a 10% to 50% recovery by the next dose (ie, breakthrough DNA synthesis). DNA synthesis recovery appeared to be inversely related to the dose administered. Only at the MTD (52 mg/m^2/day) and higher was DNA synthesis inhibition maintained throughout the dosing interval.

3.7. Summary and Conclusions for Phase I Study of Clofarabine

ID99-383 was a Phase I, open-label, dose-escalating study of clofarabine administered to pediatric patients with hematologic malignancies, specifically ALL and AML, who failed standard therapy or for whom no such therapy existed.

According to the published results, the DLT in this study was hepatic toxicity (hyperbilirubinemia and elevated transaminase levels) and skin rash observed at the 70 mg/m^2/day dose level.[59] The MTD was determined by the investigator to be 52 mg/m^2/day IVI (for 1 hour in the original protocol but later amended to be increased to 2 hours or up to 3 hours as needed) $\times$ 5 days for pediatric patients with refractory or relapsed acute leukemia.[59] ILEX evaluated the data retrospectively and agreed with the investigator's

determination of the MTD (52 mg/m^2/day) as the safe dose for Phase II studies in pediatric patients with ALL and AML.

The investigators determined that complete or partial responses were observed in 8/25 (32%) patients, with some hematologic improvement noted in another 7/25 (28%) patients. Specifically, 5/25 (20%) patients achieved a complete remission and 3/25 (12%) patients achieved a PR. Among the patients who achieved a complete response, 4 were diagnosed with ALL (1 received 30 mg/m^2/day, 2 received 40 mg/m^2/day, and 1 received 70 mg/m^2/day decreased to 52 mg/m^2/day at the time of response) and 1 was diagnosed with AML (52 mg/m^2/day). Among those who obtained a partial response, 2 were diagnosed with AML (40 mg/m^2/day) and 1 was diagnosed with ALL (52 mg/m^2/day). The IRRP determined that according to the Phase II response criteria, the 5 investigator-assessed CRs were 2 CRs, 1 CRp, and 2 PRs.

Overall, these results indicate that clofarabine has the potential to induce benefit with manageable toxicity at a dose of 52 mg/m^2/day administered for 5 days per cycle.

4. PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

4.1. Data Availability

Table 6 presents a summary of human pharmacokinetic studies in both adults and children. Pharmacokinetic data were available from 93 patients, of which 40 (16 AML and 24 ALL) were pediatric patients. In study ID99-383, 10 patients had ALL and 2 patients had AML. All patients in study CLO-212 had ALL and all patients in study CLO-222 had AML.

Table 6: Tabular Summary of Human Pharmacokinetic Studies

Protocol Number	Country	Phase	N[1]	Ages/Sex[2]	Cancer Type	Doses (per day)	Lot Number	Regimen	Primary Objective	Year Study Complete
DM93-036	USA	I	51/40	19 - 79; 18 M/22 F	Adults; Solid and hematologic malignancies	2 to 52 mg/m^2	254I0493 009I0100 173I0601A 173I0601B 324I1101	IVI for 1 hour every day for 5 days every 3 to 4 weeks; max. 12 cycles	Determine MTD; safety; pharmacokinetics	2001
ID99-383	USA	I	25/12	3 – 17; 6 M/6 F 10 ALL/ 2 AML	Pediatrics; Hematologic malignancies	11.25 to 70 mg/m^2	173I0601A 173I0601B 009I001 324I1101 N12008F	IVI for 1 to 3 hours every day for 5 days every 2 to 6 weeks; max. 12 cycles	Determine MTD; safety; pharmacokinetics	2002
CLO-212	USA	II	40/14[3]	2 – 17; 7 M/7 F	Pediatrics; ALL	52 mg/m^2	CTM02059 ICJ001 N12008F C03E015	IVI for 2 hour every day for 5 days every 2 to 6 weeks; max. 12 cycles	Efficacy; pharmacokinetics; safety	Ongoing

Table 6: Tabular Summary of Human Pharmacokinetic Studies (continued)

Protocol Number	Country	Phase	N[1]	Ages/Sex[2]	Cancer Type	Doses (per day)	Lot Number	Regimen	Primary Objective	Year Study Complete
CLO-221	USA	II	40/13	32 - 78; 7 M/6 F	Adults; AML	40 mg/m^2	N12008F CTM02059 ICJ001	IVI for 1 hour every day for 5 days every 28 days; max. 6 cycles	Efficacy; pharmacokinetics; Safety	2003
CLO-222	USA	II	30/14[3]	3 – 19; 8 M/6 F	Pediatrics; AML	52 mg/m^2	CTM02059 ICJ001 C03E015	IVI for 2 hour every day for 5 days every 2 to 6 weeks; max. 12 cycles	Efficacy; pharmacokinetics; safety	Ongoing

[1] Denotes the number of patients enrolled who received study drug and the number of patients for which pharmacokinetic data were collected.
[2] Ages and sex of patients for whom pharmacokinetic data were collected.
[3] Indicates number available at time of database lock.

4.2. Pharmacokinetic and Statistical Methods

Pharmacokinetic data in studies CLO-212 and CLO-222 were analyzed within each individual study using noncompartmental pharmacokinetic analysis methods with WinNonlin Professional, Version 4.0 (Pharsight Corp., Mountain View, CA). Clofarabine and clofarabine triphosphate pharmacokinetic data from study ID99-383 were analyzed using descriptive statistics only because of the sparse and unstructured nature of the data. Clofarabine pharmacokinetic data from studies ID99-383, CLO-212, and CLO-222 were pooled and analyzed using population pharmacokinetic methods with NONMEM (Globomax LLC, Hanover, MD). Clofarabine triphosphate data from study ID99-383 were included in the population analysis to develop a joint parent-metabolite pharmacokinetic model.

4.3. Pharmacokinetic and Pharmacodynamic Results

Table 7 presents a summary of clofarabine pharmacokinetics after single-dose administration while Table 8 presents the results after multiple dose administration. Tables 7 and 8 present pharmacokinetic data from studies CLO-212, CLO-221, and CLO-222 only, as these were the only studies in which structured sampling was done and pharmacokinetic parameters could be estimated using noncompartmental analysis.

Table 7: Tabular Pharmacokinetic Parameter Estimate Summary After Single Dose Administration

Protocol Number	Study Design	Systemic Clearance (L/h)	Vdss (L)	Renal Clearance (L/h)	AUC(0-¥) (ng*h/mL)	% of Dose Excreted in Urine	Cmax (ng/mL)	Half-life (h)
CLO-212	Pediatrics; rich data; plasma and urine	43.2 (16.5 - 78.7)	251.0 (81.4 – 474.6)	28.9 (1.1 – 86.0)	1726 (1026 – 3156)	48.5 (7.8 – 82.2)	403.1 (140.9 – 765.8)	4.7 (2.2 – 8.6)
CLO-221	Adults; rich data; plasma and urine	30.6 (15.2 – 64.9)	173.1 (106.7 – 293.6)	17.7 (4.2 – 46.8)	2618 (1172 – 3875)	58.3 (28.1 – 141.3)	620.5 (235.0 – 1923.1)	6.2 (4.1 – 8.6)
CLO-222	Pediatrics; rich data; plasma and urine	38.9 (13.9 – 70.4)	274.4 (85.3 – 540.8)	26.6 (2.1 – 25.9)	2044 (1344 – 2780)	60.6 (9.3 – 135.5)	417.5 (156.9 – 1048.9)	5.7 (3.6 – 10.3)

Data reported as mean (range).

Table 8: Tabular Pharmacokinetic Parameter Estimate Summary At Steady-State After 5 Days of Once-Daily Dosing

Protocol Number	Study Design	Renal Clearance (L/h)	% of Dose Excreted in Urine	Cmax (ng/mL)	Accumulation Ratio based on AUC(0-8)
CLO-212	Pediatrics; rich data; plasma and urine	28.9 (1.1 – 86.0)	48.5 (7.8 – 82.2)	558.9 (214.2 – 1389.8)	1.25 (0.51 – 1.72)
CLO-221	Adults; rich data; plasma and urine	25.3 (2.1 – 56.5)	52.8 (26.5 – 77.0)	516.9 (231.3 – 797.3)[1]	Not calculated
CLO-222	Pediatrics; rich data	34.7 (3.9 – 68.9)	69.4 (26.4 – 113.4)	471 (249 – 748)	1.40 (0.82-1.99)

Data reported as mean (range).
[1] indicates that data reported are the mean and range from the end of infusion summary statistics on Day 5.

The population pharmacokinetics of clofarabine were studied in 40 pediatric patients ages 2 to 19 years old (21 males/19 females) with relapsed or refractory acute lymphocytic leukemia or acute myelogenous leukemia given multiple doses. Clofarabine pharmacokinetics were weight-dependent, although IVI of 52 mg/m^2/day produced equivalent exposure across a wide range of weights. For example, in study CLO-212 the range of weights in patients who had pharmacokinetic sampling done was 14.1 kg to 74.7 kg. The coefficient of variation in Cmax and AUC(0-∞) was 55% (37% after removal of 1 patient with a high, possibly aberrant value) and 24%, respectively. Hence, despite such wide variability in weight, variability in exposure was relatively small.

Based on nonlinear mixed effects modeling using NONMEM, two covariates were shown to influence clofarabine pharmacokinetics: weight, which affected all pharmacokinetic parameters and was the most influential covariate, and WBC count, which affected only central volume. Clofarabine pharmacokinetics were best described by a 2-compartment model with a systemic clearance of 32.8 L/h (27% between-subject variability) in a 40 kg child. Volume of distribution and half-life were also dependent on the patient's WBC count. Clofarabine had a β-half-life of 6.4 hours in a 40 kg person having a WBC count of $10 \times 10^3/\mu L$. Clofarabine was 47% bound to plasma proteins, predominantly to albumin, and had a volume of distribution at steady-state in a 40 kg person having a WBC count of

$10 \times 10^3/\mu L$ of 210 L (72% between-subject variability), indicating extensive tissue distribution.

In accordance to allometric principles, weight positively affected clofarabine clearance terms and volume of distribution. Based on noncompartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 $L/h/m^2$ and 172 L/m^2, respectively. Decreasing weight would be expected to increase Cmax and decrease AUC(0-∞).

Besides weight, the only other covariate identified as influencing clofarabine pharmacokinetics was WBC count, which positively affected central volume. With repeated administration of clofarabine, WBC count decreases. Thus, clofarabine AUC(0-∞) would be expected to decrease while Cmax would be expected to increase as WBC count is depleted. However, this change is likely to be of little significance for many reasons. First, a bottle-neck exists between clofarabine and the formation of clofarabine triphosphate such that increases or decreases in clofarabine do not necessarily translate to increases or decreases in clofarabine triphosphate. Second, no relationship between clofarabine exposure (AUC, Cmax, clearance, and total dose) and response or toxicity (anxiety, dyspnea, hypotension, nausea or vomiting, neutropenia, sepsis, and death) was observed, as would be expected for an inactive prodrug. Hence, dose adjustment based on WBC count does not appear warranted at this time.

No apparent difference in clofarabine pharmacokinetics was observed between patients with ALL or AML (see Tables 6 and 7, study CLO-212 vs. CLO-222). For example, Cmax after single dose administration of 52 mg/m^2 ranged from 141 ng/mL to 766 ng/mL with an average of 403 ng/mL in pediatric patients with ALL (n = 24) and from 157 ng/mL to 1049 ng/mL with an average of 418 ng/mL in patients with AML (n = 16). This result was not unexpected as no nucleoside has shown pharmacokinetic differences in this population.

No difference was observed in the pharmacokinetics between males and females. For example, AUC(0-∞) after single dose administration of 52 mg/m^2 ranged from

1026 ng*h/mL to 2780 ng*h/mL with an average of 1749 ng*h/mL in males (n = 11) and from 1281 ng*h/mL to 3156 ng*h/mL with an average of 2018 ng*h/mL in females (n = 10). Other evidence of this result was in the population analysis where sex was not identified as an influential covariate. Lastly, after controlling for weight, age-related changes in clofarabine pharmacokinetics were not identified in patients 2 to 19 years old.

Clofarabine showed balanced systemic clearance through a combination of renal and non-renal elimination. Clofarabine total systemic clearance was estimated at 28.8 L/h/m^2 and was proportional to body weight. About 57% of the dose was excreted in urine in a 24 hour period resulting in a renal clearance of 10.8 L/h/m^2. Clofarabine showed evidence of filtration and tubular secretion (possibly through the human organic anion transporter, hOAT) as kidney elimination mechanisms.

Because of the limited sampling design and few number of patients studied, clofarabine triphosphate concentrations were essentially constant over the sampling period having an estimated concentration of 11.6 ± 0.3 µM. The in vivo half-life of clofarabine triphosphate in peripheral mononuclear cells could not be definitively established but was estimated to be at least 24 hours. No relationship between clofarabine or clofarabine triphosphate exposure and toxicity or response could be developed in this population.

Limited pharmacokinetic data are available in adults. Clofarabine showed dose proportionality between 2 and 55 mg/m^2 when infused over 1 to 2 hours. Clofarabine total systemic clearance was estimated at 30.6 L/h, smaller than pediatric patients, with 53% to 58% of the dose excreted in urine as parent clofarabine (about the same as pediatric patients). Clofarabine renal clearance was about 16.5 L/h, smaller than pediatric patients. Clofarabine total volume of distribution at steady-state averaged 173 L, smaller than pediatric patients, and had a β-half-life of 6.2 hours (slightly longer than pediatric patients). Little accumulation was observed with once-daily administration. The net effect of these small differences in pharmacokinetics between adults and children was that even with adults receiving a smaller dose (40 mg/m^2/day vs 52 mg/m^2/day), exposure in adults was greater (Table 9).

Table 9: Tabular Pharmacokinetic Parameter Estimate Summary For Pediatric and Adult Patients With Acute Leukemias

	CLO-212 Pediatrics with ALL	**CLO-222 Pediatrics with AML**	**CLO-221 Adults**
N	14	14	13
Dose (mg/m^2/day)	52	52	40
Dose Range (mg)	45 – 134	31.7 – 95.0	59 – 106
Weight (kg)	45.0 [36.9] (15.6 – 129.8)	48.4 [52.5] (14.1 – 74.7)	78.8 [76.0] (55 – 145.3)
BSA (m^2)	1.32 [1.22] (0.65 – 2.58)	1.40 [1.56] (0.61 – 1.82)	1.87 [1.83] (1.47 – 2.64)
Age (years)	11.4 [12.0] (2 – 17)	12.3 [12.5] (2 – 19)	55.6 [57.0] (32 – 78)
Cmax (ng/mL)	403 [380] (141 – 766)	418 [360] (157 – 1049)	620.5 [487] (235 – 1923)
AUC(0-∞) (ng*h/mL)	1726 [1709] (1026 – 3156)	2044 [1930] (1344 – 2780)	2618 [2726] (1172 – 3875)
Clearance (L/h)	43.2 [42.5] (16.5 – 78.7)	38.9 [37.6] (13.9 – 70.4)	30.6 [28.1] (15.2 – 64.9)
Clearance ($L/h/m^2$)	33.1 [30.4] (16.5 – 50.7)	26.8 [27.0] (18.7 – 38.7)	17.2 [14.6] (10.4 – 34.1)
Renal Clearance (L/h)	28.9 [22.2] (1.1 – 86.0)	26.6 [25.9] (2.1 – 64.1)	17.7 [17.0] (4.2 – 46.8)
Renal Clearance ($L/h/m^2$)	18.3 [13.7] (0.8 – 53.8)	17.7 [17.0] (1.4 – 37.7)	9.5 [8.6] (2.6 – 25.6)
Vdss (L)	251 [209] (81 – 475)	274 [239] (85 – 541)	173 [144] (107 – 294)
Vdss (L/m^2)	187 [156] (86 – 303)	182 [167] (96.2 – 297.2)	98.9 [75.8] (55.7 – 154.5)
Half-life (hours)	4.7 [4.3] (2.2 – 8.6)	5.7 [4.9] (3.6 – 10.3)	6.2 [6.2] (4.1 – 8.6)

Pharmacokinetic parameters are reported as mean [median] (range). Pharmacokinetic values are after single dose administration.

These differences in clofarabine pharmacokinetics between adults and children did not appear to translate to differences in intracellular clofarabine triphosphate concentrations. Average clofarabine triphosphate concentrations in pediatric patients receiving 52 mg/m^2 were about 16 µM with a range of 2.9 µM to 42 µM. In adults receiving 40 mg/m^2 clofarabine, clofarabine triphosphate concentrations ranged from less than 1 µM to 44 µM. Further, the half-life of clofarabine triphosphate was estimated to be at least 24 hours in adults, the same as in pediatric patients. In patients where clofarabine triphosphate concentrations were serially assessed during the first cycle of therapy, breakthrough DNA

synthesis was observed at doses less than 40 mg/m^2/day, similar to pediatric patients. For example, 60% DNA synthesis inhibition was observed at the end of infusion after a single dose in a patient dosed at 22.5 mg/m^2/day. But breakthrough DNA synthesis occurred before the second dose such that DNA synthesis was inhibited by only 45% relative to baseline values. This pattern was repeated for two more days. In a patient dosed at 55 mg/m^2/day, DNA synthesis was inhibited more than 95% and remained inhibited with no breakthrough synthesis observed on subsequent days. These results lend further support for the choice of doses used in the Phase II adult and pediatric studies.

4.4. Pharmacokinetic and Pharmacodynamic Summary and Conclusions

Clofarabine pharmacokinetics were dose proportional over the range of doses studied in both pediatric and adult patients and showed stationary pharmacokinetics with no evidence of time-dependent pharmacokinetics. No difference was observed in the pharmacokinetics between patients with ALL and patients with AML or between males and females. After controlling for weight, age-related changes in pharmacokinetics between patients 2 to 19 years old were not observed. Clofarabine was rapidly cleared from the blood having a half-life of about 6 hours and was removed through a combination of renal (filtration and tubular secretion) and hepatic elimination (~50:50). To become active, clofarabine must diffuse or be transported into the cell whereupon it must be sequentially phosphorylated, first by deoxycytidine kinase and then by unknown kinases, to the triphosphate metabolite. Unlike fludarabine, the rate-limiting step in the formation of the triphosphate is the formation of the di-phosphate from the monophosphate, ie, deoxycytidine kinase is not the rate-limiting step in the triphosphate's formation.

Clofarabine triphosphate is a potent competitive inhibitor (K_i of 1 μM) of DNA polymerase α and competes with dATP for incorporation into DNA. In addition, DNA elongation and/or repair are impaired by the incorporation of clofarabine monophosphate into the DNA through chain termination and strand breakage. Although clofarabine is rapidly cleared from the blood, the half-life of intracellular clofarabine triphosphate is much longer and although the exact value could not be reliably determined, the half-life of clofarabine triphosphate was

estimated to be greater than 24 hours. Only at doses greater than 40 mg/m^2/day are quantifiable clofarabine triphosphate concentrations observed at predose upon repeated dosing. Further, it is only at doses greater than 40 mg/m^2/day does breakthrough DNA synthesis not occur, further underscoring the rationale for the clinical dose of 52 mg/m^2/day.

5. STUDY INFORMATION AND RESULTS FROM THE PIVOTAL PHASE II TRIALS

Data discussed in this section are based on the 84 pediatric patients ages 1 to 22 (≤21 at time of initial diagnosis) from the 2 multicenter, open-label Phase II studies (CLO-212 and CLO-222) conducted by ILEX. The 84 patients discussed in the efficacy section differs from the 113 patients discussed in the integrated safety population because the integrated population includes the 25 ALL/AML patients from the Phase I trial (ID99-383) as well as 4 pediatric patients who were included in the clofarabine adult trials. Safety data are discussed in Section 6.

Two pivotal Phase II studies have been conducted by ILEX in pediatric patients with refractory or relapsed ALL (CLO-212, 49 patients) or refractory or relapsed AML (CLO-222, 35 patients), in which clofarabine was used as a single agent. Both studies were Phase II, open-label, nonrandomized, fixed-dose studies in refractory or relapsed acute pediatric leukemia. The dose selected for these 2 pivotal studies was 52 mg/m^2/day, based upon the safety profile in the Phase I/II pediatric study (ID99-383), as well as the pharmacokinetic/ pharmacodynamic-dose relationships. The 2 pivotal studies will be discussed individually in Section 5.1 (CLO-212) and Section 5.2 (CLO-222), as the prognosis and response for patients with these diseases differs. Data from the 2 pivotal studies are combined in Section 5.3 and the overall conclusions in Section 5.4 to demonstrate how many patients benefited from clofarabine single-agent therapy in these trials.

5.1. Patients with ALL (CLO-212)

5.1.1. Study Objectives and Design (CLO-212)

The primary objective of this study was to determine the OR rate (CR + CRp) of clofarabine in pediatric patients with refractory or relapsed acute lymphocytic leukemia (ALL). Secondary objectives included documenting the rate of complete remission (CR), complete remission in the absence of total platelet recovery (CRp), and partial remission (PR); duration of remission and overall survival (OS); safety profile and tolerability of clofarabine for this

population and dosing regimen; and the pharmacokinetic profile and intracellular pharmacology and metabolism of clofarabine in selected patients.

This was a Phase II, non-randomized, open-label, single-arm study of clofarabine administered to pediatric patients with refractory or relapsed ALL who were not eligible for therapy of higher curative potential. Patients were to be treated with clofarabine 52 mg/m^2/day by IVI over 2 hours for 5 consecutive days repeated every 2 to 6 weeks for up to 12 cycles dependent on recurrence of leukemia or recovery of normal hematopoiesis (ANC $\geq 0.75 \times 10^9$/L). Patients who achieved a CR were eligible to receive a HSCT. As these patients were at high risk of relapse, and because of HSCT scheduling logistics, many investigators had these patients proceed to transplant as soon as there was complete or even substantial clearance of bone marrow blasts without allowing for full peripheral blood count recovery or waiting to undergo additional cycles of clofarabine. The implication of this practice pattern is that some of these patients could have become a CRp or CR given sufficient time for recovery of blood counts or additional cycles of clofarabine.

The investigator was to determine the date of relapse for each patient based on the protocol definitions. Safety was to be evaluated based on incidence, severity, duration, causality, seriousness, and type of AEs; and changes in the patient's physical examination, vital signs, and clinical laboratory results. Investigators were to grade the severity of AEs using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC), version 2.0 (published 30 April 1999).

Patients were to have a diagnosis of ALL according to the French American British (FAB) classification with ≥25% blasts in the bone marrow; have been 21 years old or younger at the time of initial diagnosis; not eligible for therapy of higher curative potential, and been in second or subsequent relapse and/or refractory.

The results were to be analyzed on an intent-to-treat (ITT) basis. All patients who received any clofarabine were included in the safety and efficacy analyses. Final determination of response was to be made by an IRRP.

5.1.2. Patient Disposition (CLO-212)

Of the 49 patients in CLO-212, the most common reason (20 patients, 40.8%) for discontinuation of treatment with clofarabine was failure to achieve response after 2 cycles. The second most frequent reason for discontinuation was disease progression, which occurred in 9 (18.4%) patients, followed by patient scheduled to receive transplant (4 patients, 8.2%), and investigator decision, refusal of further treatment, death due to AE, and death due to other causes occurred in 3 patients each (6.1%).

5.1.3. Patient Demographics (CLO-212)

The median age of patients treated in CLO-212 was 12, with the highest percentage of patients occurring in the 2 to 12 year-old age group. The 12 to 16 and 16 to 22 age groups were almost equally represented, with the fewest patients occurring in the 0 to 2 year old group, only 3 patients (6.1%). There were more males than females, and the majority of patients were either Caucasian or Hispanic. See Table 10.

Table 10: Demographics at Baseline (CLO-212)

Variable		**ITT Patients (N=49)**
Age (years):	N	49
	Mean	12.18
	Median	12
	Standard deviation	5.12
	Minimum	1
	Maximum	20
Age Category:	0 to ≤2	3 (6.12%)
	>2 to ≤12	22 (44.90%)
	>12 to ≤16	11 (22.45%)
	>16 to ≤22	13 (26.53%)
Sex:	Female	20 (40.82%)
	Male	29 (59.18%)
Ethnicity:	Caucasian	20 (40.82%)
	Hispanic	20 (40.82%)
	Other	3 (6.12%)
	Black	6 (12.24%)

5.1.4. Other Baseline Characteristics (CLO-212)

5.1.4.1. Prior Induction Therapies (CLO-212)

Seventeen patients (34.7%) in CLO-212 underwent 2 prior induction therapies, and 17 patients (34.7%) underwent 3 prior induction therapies. Patients in this study had to have received at least 2 prior induction therapies, and some patients received as many as 6. The median number of prior induction regimens was 3. See Table 11.

Table 11: Prior Induction Therapies (CLO-212)

Number of Prior Induction Regimens	ITT Patients (N=49)	
	n	%
2	17	34.7
3	17	34.7
4	12	24.5
5	1	2.0
6	2	4.1

5.1.4.2. Prior Transplants (CLO-212)

Almost a third of the patients in this study had received a prior transplant and 2 patients had received 2 prior transplants. See Table 12.

Table 12: Prior Transplants (CLO-212)

Number of Prior Transplants	ITT Patients (N=49)	
	n	%
0	34	69.4
1	13	26.5
2	2	4.1

5.1.4.3. Refractory Patients (CLO-212)

Refractory patients are defined as those who failed their most recent, non-palliative therapeutic regimen. Thirty of the 49 patients (61%) in CLO-212 were considered refractory

to their most recent prior treatment regimens. These 30 patients had undergone from 2 to 6 prior regimens, and 13 patients had been refractory to more than 1 prior regimen.

5.1.5. Extent of Exposure (CLO-212)

The number of cycles patients in this study received ranged from 1 to 8, with most patients receiving 1 or 2 cycles of clofarabine. The median number of cycles received was 2. See Table 13.

Table 13: Exposure to Study Drug by Cycle (CLO-212)

Total Number of Cycles Received	ITT Patients (N=49)	
	N	%
1	21	42.9
2	19	38.8
3	6	12.2
4	1	2.0
5	1	2.0
6	0	0
7	0	0
8	1	2.0

5.1.6. Efficacy Results (CLO-212)

Confirmation of diagnosis for both of the pivotal Phase II trials (CLO-212 and CLO-222) was obtained from an independent pathologist with expertise in hematologic malignancies. In addition, an IRRP was used in both trials. The IRRP was comprised of 3 pediatric oncologists who were otherwise not participants in the study; their role was to confirm the response for each patient. Confirmation of response was based on a review of the patient's bone marrow aspirate reports and peripheral blood counts.

5.1.6.1. Efficacy Parameters Used to Establish Response (CLO-212)

The response criteria (CR, CRp, and PR), failures, and relapses were based on COG response criteria and were agreed to by the FDA. The rationale for CRp was that the lack of platelet recovery likely reflected bone marrow toxicity from previous therapy or possibly clofarabine.

Additionally, the lack of platelet recovery in this patient population was not considered a reflection of lack of efficacy. The investigator was to determine the date of relapse for each patient based on the protocol definitions.

Responses in CLO-212 were assessed according to the criteria listed below:

Response Criteria for Patients with ALL (CLO-212)

Response Category	Response Criteria
CR	• No evidence of circulating blasts or extramedullary disease • M1 bone marrow (≤5% blasts) • Recovery of peripheral counts (platelets ≥100 × 10^9/L and ANC ≥1.0 × 10^9/L)
CRp	• Meets all of the criteria for a CR except platelet recovery to ≥100 × 10^9/L
PR	• Complete disappearance of circulating blasts • M2 bone marrow (>5% and ≤25% blasts) and appearance of normal progenitor cells • M1 marrow that does not qualify for CR or CRp
Treatment failures	• All other responses

Although patients with an M2 marrow and patients with an M1 marrow can both qualify as a PR, there is a qualitative difference between these two types of PRs. A patient who is a PR by definition but has an M1 marrow could potentially achieve a response of CRp or CR if given time for ANC recovery. This type of PR may be more indicative of efficacy than patients who are a PR but have an M2 bone marrow, even though patients with a PR and an M2 marrow may also benefit from proceeding to transplant.

The importance of responses in the pivotal Phase II trials that were assessed as PRs is addressed in detail in Section 5.2.6.2.

5.1.6.2. Objective Response Rates (CLO-212)

According to the IRRP, 6 patients (12.2%) achieved a CR, 4 patients (8.2%) achieved a CRp, and 5 patients (10.2%) achieved a PR. The OR rate (CR+CRp) was 20.4% (95% CI: 10% to

34%), and 15 patients (30.6%) achieved at least a PR (95% CI: 18% to 45%). The investigators' determination of response is also provided in Table 14 below.

Table 14: Best Objective Response (CLO-212, All Patients)

	ITT Patients (N=49)			
	Investigator Assessment		Independent Panel Assessment	
Response Category	**N**	**%**	**N**	**%**
Complete Remission (CR)	6	12.2	6	12.2
Complete Remission/Absence of Total Platelet Recovery (CRp)	4	8.2	4	8.2
Partial Remission (PR)	4	8.2	5	10.2
Treatment Failure	28	57.1	26	53.1
Not Evaluable	6	12.2	8	16.3
Not Assessed	1	2.0		
Overall Remission (CR + CRp)	10	20.4	10	20.4
CR + CRp + PR	14	28.6	15	30.6

95% Confidence Interval for IRRP Rate of Overall Remission (CR + CRp): (0.10, 0.34).
95% Confidence Interval for IRRP Rate of Any Remission (CR + CRp + PR): (0.18, 0.45).

Though not included in the calculation of OR rate or duration of remission, an additional patient was considered by the investigator to have benefited from clofarabine treatment. This patient entered the study with 93% blasts, but after 2 cycles of clofarabine the investigator assessed the patient as a PR based on the bone marrow specimen and circulating blasts. The IRRP assessed this patient's response as not evaluable due to the poor quality of the bone marrow specimen they received. Nonetheless, this patient proceeded to receive a MUD transplant approximately 1 month after treatment with clofarabine for a post-transplant survival of 29.7+ weeks and overall survival of 40.1+ weeks.

5.1.6.3. Duration of Remission (CLO-212)

Duration of remission was calculated from the IRRP-determined start of response to first objective evidence of relapse or death, including continued remission for those patients who proceeded to transplant post-clofarabine treatment. The median duration of remission had not yet been reached for patients who achieved a CR as half of the 6 patients were still in

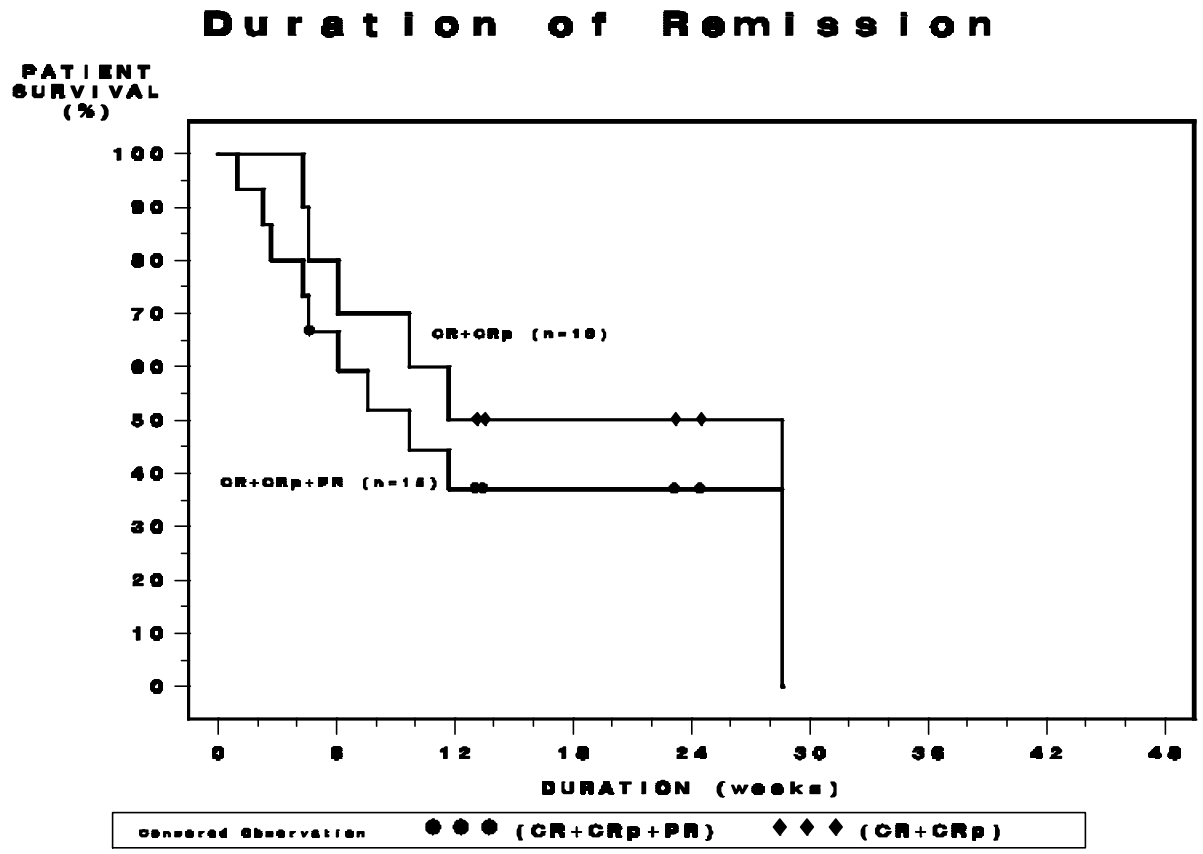
remission. Remission ranged from a minimum of 4.3 weeks to a maximum of 24.4+ weeks. The median duration of remission for patients who achieved a CRp was 20.2 weeks (95% CI: 4.6 to 28.6 weeks). For patients who achieved a PR the median duration of remission was 2.7 weeks (95% CI: 1.0 to 7.6 weeks). The median duration of remission for the OR rate was 20.2 weeks (95% CI: 6.1 to 28.6 weeks) and for patients who achieved at least a PR it was 9.7 weeks (95% CI: 4.6 to 28.6 weeks). See Table 15.

Table 15: Duration of Remission (weeks) for Patients in CLO-212

Response Category (IRRP)	N	Kaplan-Meier Median	Lower Limit of 95% CI	Upper Limit of 95% CI	Minimum	Maximum	% Censored[1]
Complete Remission	6	.	6.1	.	4.3	24.4+	50.0
Complete Remission w/o Platelet Recovery	4	20.2	4.6	28.6	4.6	28.6	25.0
Partial Remission	5	2.7	1.0	7.6	1.0	7.6	20.0
Overall Remission (CR+CRp)	10	20.2	6.1	28.6	4.3	28.6	40.0
Complete or Partial Remission (CR+CRp+PR)	15	9.7	4.6	28.6	1.0	28.6	33.3

[1] Percentage of patients still in remission at data cutoff

Kaplan-Meier duration of remission curves for CLO-212 are presented by OR and any remission in the figure below.



CLO-212: G:\...\DURATION_OVERLAY.SAS

5.1.6.4. Survival (CLO-212)

Survival was calculated from the first dose of clofarabine to death or the date of last follow up. Median survival had not yet been reached for patients who achieved a CR as 5 of the 6 patients were still alive. Survival ranged from a minimum of 10.4+ weeks to a maximum of 58.6 weeks at the time of data cutoff. The median survival for patients who achieved a CRp was 42.0 weeks (95% CI: 9.1 weeks to upper limit not estimated), and was 29.7 weeks (95% CI: 7.0 to 36.3 weeks) for patients who achieved a PR. For patients who achieved a CR + CRp, the median survival was 58.6 weeks (95% CI: 42.0 weeks to upper limit not estimated), and for patients who achieved at least a PR the median survival was 42.0 weeks (95% CI: 29.7 weeks to upper limit not estimated). See Table 16. The Kaplan-Meier curves for survival for CLO-212 are presented in the Executive Summary.

Table 16: Survival (weeks) for Patients with ALL (CLO-212)

Response Category (IRRP)	N	Kaplan-Meier Median	Lower Limit of 95% CI	Upper Limit of 95% CI	Minimum	Maximum	% Censored[1]
Complete Remission	6	58.6	.	.	10.4+	58.6	83.3
Complete Remission w/o Platelet Recovery	4	42.0	9.1	.	9.1	63.1+	50.0
Partial Remission	5	29.7	7.0	36.3	7.0	36.3	20.0
Treatment Failure/Not Evaluable	34	7.4	6.3	11.7	0.9	40.1+	8.8
Overall Remission (CR+CRp)	10	58.6	42.0	.	9.1	63.1+	70.0
Complete or Partial Remission (CR+CRp+PR)	15	42.0	29.7	.	7.0	63.1+	53.3
All Patients	49	11.7	7.1	18.4	0.9	63.1+	22.4

[1] Percentage of patients still alive at data cutoff

5.1.6.5. Post-Treatment Transplant (CLO-212)

In this study, 8/49 patients (16.3%) went on to receive a transplant after clofarabine treatment. All but 1 of these patients was male. Patient ages ranged from 2 to 18 and they received either 2 or 3 cycles of clofarabine. Time to transplant after clofarabine treatment ranged from 16 days to 77 days, indicating that these patients proceeded to transplant very quickly. Five of the 8 patients who proceeded to transplant were still alive at data cutoff. Their survival post treatment with clofarabine ranged from 17.6 weeks to 63.1+ weeks, and their survival post transplant ranged from 3.9+ weeks to 43.1+ weeks. It is noteworthy that of these 8 patients, 2 each had achieved a CR, CRp, and PR, and the other 2 were treatment failure or not evaluable. It is worth noting that transplants have been reported to benefit children with ALL in second or later remission, and in patients classified as a high risk for relapse.[60,15,16,18,61] See Table 17 for transplant information.

Table 17: Patients Who Proceeded to Transplant After Clofarabine Treatment (CLO-212)

Sex (Age)	# of Cycles of Clofarabine	Determination of Response IRRP/Investigator	Days to Transplant Post-Clofarabine[1]	Initial Post-Transplant Bone Marrow	Alive (Y/N)	Survival from Start of Clofarabine[2] (weeks)	Survival Post-Transplant[3] (weeks)
Male (17)	3	CR/CRp	28	3% blasts normocellular	Yes	44.0+	29.9+
Female (11)	2	CR/CR	63	NA	Yes	17.6+	3.9+
Male (2)	3	CRp/CRp	77	2% blasts hypercellular	Yes	63.1+	43.1+
Male (12)	2	CRp/CRp	37	5% blasts hypocellular	No	42.0	32.3
Male (18)	2	PR/PR M1 marrow 4.5% blasts	22	1% blasts	Yes	22.9+	16.1+
Male (6)	2	PR/PR M1 marrow 0% blasts	16	5% blasts hypercellular	No	29.7	22.9
Male (12)	2	NE/PR no cells counted	52	NA	Yes	40.1+	29.7+
Male[4] (7)	2	TF/TF	26	1% blasts	No	17.9	10.6

[1] Time from the date of last dose of clofarabine to date of transplant.
[2] Time from the date of first dose of clofarabine to death or last follow-up.
[3] Time from the date of transplant to death or last follow-up.
[4] This patient was not in remission following treatment with clofarabine, and is not included in the clinical benefit analysis.

It is noteworthy that 2 patients who, according to the IRRP and the investigator, achieved a PR with clofarabine treatment proceeded to transplant post clofarabine. For example, an 18 year-old male received 2 cycles of clofarabine at 52 mg/m^2/day and had a decrease in bone marrow blasts from 81% at study entry to 15% after cycle 1 and to 4.5% after cycle 2. He proceeded quickly to transplant without receiving additional clofarabine treatment. Less than 2 weeks after transplant, he had 0.5% blasts. As of the last follow up, his duration of remission was 4.6+ weeks, post-transplant survival was 16.1+ weeks, and overall survival was 22.9+ weeks.

In addition, the "not evaluable" patient previously described in Section 5.1.6.2 also proceeded to transplant as an investigator-determined PR, although the IRRP determined the

response as not evaluable due to poor quality marrow specimen. This patient had undergone a prior PBSCT MUD transplant + TBI prior to treatment with clofarabine. At study entry he had 93% blasts. After 2 cycles of clofarabine the investigator determined the patient was a PR according to the bone marrow specimen and circulating blasts; however, the IRRP determination was "not evaluable." This patient proceeded to transplant 1 month after end of study with post-transplant survival of 29.7+ weeks and overall survival of 40.1+ weeks. Although this occurred in only 1 patient from CLO-212, the data suggest that a PR may be a benefit when combined with transplant. The later discussion of efficacy for CLO-222 (Section 5.2.6) revisits this issue and supports the value of taking a patient with a PR to transplant.

5.1.6.6. Refractory Patients (CLO-212)

Of the 30 patients (61.2%) who were refractory to their last prior chemotherapy, the IRRP determined that 3 patients (10%) achieved a CR, 2 patients (6.7%) achieved a CRp, and 2 patients (6.7%) achieved a PR. The OR rate in this population was 16.7%, and the response rate for patients who achieved at least a PR was 23.3%. See Table 18.

Table 18: Best Objective Response for Refractory Patients (CLO-212)

(Last Prior Chemotherapy Response was Either Treatment Failure or Not Evaluable)				
	N=30			
	Investigator Assessment		Independent Panel Assessment	
Response Category	**n**	**%**	**n**	**%**
Complete Remission (CR)	3	10.0	3	10.0
Complete Remission /Absence of Total Platelet Recovery (CRp)	2	6.7	2	6.7
Partial Remission (PR)	1	3.3	2	6.7
Treatment Failure	20	66.7	19	63.3
Not Evaluable	4	13.3	4	13.3
Overall Remission (CR + CRp)	5	16.7	5	16.7
CR + CRp + PR	6	20.0	7	23.3

95% Confidence Interval for IRRP Rate of Overall Remission (CR + CRp): (0.06, 0.35)

The number and variety of prior regimens these patients had received is worth noting. Most of these patients had undergone several prior multi-drug chemotherapeutic regimens. Table 19 below presents the prior regimen information for some patients as well as their response to clofarabine treatment.

Table 19: Refractory Patients' Prior Regimens and Response to Clofarabine (CLO-212)

PT ID	IRRP Response/ Investigator Response	Number of Prior Regimens	Most Recent Prior Regimen (Number of Cycles)	Clofarabine Dose/ (Number of Cycles)
12-year-old Male	CR/CR	4	etoposide, ifosfamide, carboplatin (1 cycle)	52 mg/m^2/day (1) 39 mg/m^2/day (1)
18-year-old Female	CR/CR	3	cytarabine, idarubicin (1 cycle)	52 mg/m^2/day (3)
16-year-old Male	CR/CR	4	vincristine (1 cycle)	52 mg/m^2/day (2) 35 mg/m^2/day (1) 26 mg/m^2/day (5)
12-year-old Male	CRp/CRp	6	vincristine, idarubicin, decadron (1 cycle)	52 mg/m^2/day (2)
20-year-old Male	CRp/CRp	3	vincristine, cyclophosphamide, high-dose methotrexate (1 cycle)	52 mg/m^2/day (2)
3-year-old Male	PR/TF	4	etoposide, ifosfamide, MESNA (1 cycle)	52 mg/m^2/day (4)
8-year-old Female	PR/PR	4	vincristine, cytarabine, 6-thioguanine (1 cycle)	52 mg/m^2/day (3)

The median duration of remission for refractory patients who achieved a CR was 6.1 weeks (95% CI: 4.3 weeks to upper limit not estimated). Median duration of remission had not been reached for patients who achieved a CRp as 1 of these 2 patients was still alive at data cutoff. For patients who achieved a PR, the median duration of remission was 2.5 weeks (95% CI: 2.3 to 2.7 weeks). For patients who achieved CR or CRp, the median duration of remission was 6.1 weeks (95% CI: 4.3 weeks to upper limit not estimated) and for patients who achieved at least a PR it was 4.6 weeks (95% CI: 2.7 weeks to upper limit not estimated). It is worth noting that none of the refractory patients who achieved a CR and 1 of

the refractory patients who achieved a CRp did not proceed to transplant, thus for these patients remission is due entirely to treatment with single-agent clofarabine. See Table 20.

Table 20: Duration of Remission (weeks) for Refractory Patients with ALL (CLO-212)

(Last Prior Chemotherapy Response was Either Treatment Failure or Not Evaluable)							
Response Category (IRRP)	**N**	**Kaplan-Meier Median**	**Lower Limit of 95% CI**	**Upper Limit of 95% CI**	**Minimum**	**Maximum**	**% Censored[1]**
Complete Remission	3	6.1	4.3	.	4.3	24.4	33.3
Complete Remission w/o Platelet Recovery	2	.	4.6	.	4.6	23.1	50.0
Partial Remission	2	2.5	2.3	2.7	2.3	2.7	0.0
Overall Remission (CR+CRp)	5	6.1	4.3	.	4.3	24.4	40.0
Complete or Partial Remission (CR+CRp+PR)	7	4.6	2.7	.	2.3	24.4	28.6

[1] Percentage of patients still in remission at data cutoff

5.1.6.7. Patients with a Prior Transplant (CLO-212)

It should be noted that the 1 CRp patient was a 2-year-old male who had undergone 2 prior chemotherapy regimens and a BMT. He stayed in remission for 17 weeks after his second chemotherapy regimen and the prior BMT (conditioned by TBI and high-dose cytoxan). The duration of remission after clofarabine and post-clofarabine transplant was substantially longer, 28.6 weeks, than with his prior regimen and transplant. His post-clofarabine post-transplant survival was 43.1+ weeks and his overall survival after clofarabine treatment was 63.1+ weeks.

Fifteen of the 49 patients (30.6%) in this study had undergone a prior transplant. According to the IRRP, of these 15 patients 2 achieved a CR, 2 achieved a CRp, and 3 achieved a PR. The OR rate for 4/15 patients was 26.7% and the response rate for patients who achieved at least a PR (7/15) was 46.7%. See Table 21.

Table 21: Duration of Remission (weeks) for Patients with ALL Who Had a Prior Transplant

Response Category (IRRP)	N	Kaplan-Meier Median	Lower Limit of 95% CI	Upper Limit of 95% CI	Minimum	Maximum	% Censored[1]
Overall Remission (CR+CRp)	4	20.2	9.7	28.6	9.7	28.6	25.0
Complete or Partial Remission (CR+CRp+PR)	7	9.7	2.7	28.6	1.0	28.6	14.3

[1] Percentage of patients still in remission at data cutoff

5.1.7. Efficacy Conclusions (CLO-212)

Patients with ALL who enrolled in the Phase II study of clofarabine had developed highly resistant disease by study entry. In many cases, the patients had also become refractory and were no longer responding to standard agents, multi-agent combination therapy, or approaches such as myeloablative stem cell transplant. The responses to clofarabine that were observed did provide for durable disease control and also allowed selected patients with an available donor the opportunity to proceed to transplant. The previous data describe in summary form the activity of clofarabine in this highly resistant, refractory population of patients; however, details of selected patients and the impact of clofarabine on these patients may be lost when the data are presented in this manner. To illustrate the clinical benefit provided by clofarabine, a brief description of a few of the patients from CLO-212 may be useful. For example, a 16-year-old male had failed multiple prior regimens, including both a BMT and PBSCT. Just prior to entering the clofarabine trial he was given single-agent vincristine in an attempt to control his disease. Since he did not respond to vincristine, he was entered into the Phase II study of clofarabine in pediatric patients with ALL. After 2 cycles of clofarabine this patient was a CR and as of data cut-off, he had received 8 cycles of clofarabine and remained in remission for more than 24 weeks.

Another patient, a 2-year-old male had failed to achieve remission with a standard 4-drug induction regimen. He subsequently achieved remission with a regimen of cytoxan,

6-mercaptopurine, and ara-C and underwent a MUD BMT using high-dose cytoxan and TBI. He stayed in remission for a period of 17 weeks following his second remission induction and BMT before relapse was noted. Following relapse, he was entered into the Phase II clofarabine study and achieved a CRp after 2 cycles of treatment. He received a total of 3 cycles of clofarabine and eventually underwent an allogenic BMT. His remission lasted 28.6 weeks with single agent clofarabine followed by BMT, substantially longer than with his most recent previous multi-agent regimen and BMT. These data show that clofarabine provides clinical benefit in patients with highly resistant ALL.

5.1.8. Safety Results (CLO-212)

Safety results for both CLO-212 and CLO-222 are provided in Section 6.3 as part of the integrated safety assessment.

5.2. Patients with AML (CLO-222)

5.2.1. Study Objectives and Design (CLO-222)

This was a Phase II, open-label study of clofarabine administered to pediatric patients with refractory or relapsed acute myelogenous leukemia in first or subsequent relapse. Clofarabine was to be administered at 52 mg/m^2/day over 2 hours daily for 5 consecutive days repeated every 2 to 6 weeks for a maximum of 12 cycles.

The primary objective was to determine the efficacy of clofarabine in pediatric patients with refractory or relapsed AML by determining the OR rate in this patient population. The investigator was to determine the date of relapse for each patient based on the protocol definitions. An IRRP was to confirm the response for each patient.

Secondary objectives included documenting: the rate of CRs, CRps, and PRs in the study population; duration of remission and overall survival; the safety profile and tolerability of clofarabine for this population and dosing regimen; and the pharmacokinetic profile and intracellular pharmacology and metabolism of clofarabine in selected patients.

Safety was to be evaluated based on incidence, severity, duration, causality, seriousness, and type of AEs; and changes in the patient's physical examination, vital signs, and clinical laboratory results.

The results were to be analyzed on an ITT basis. All patients who received any clofarabine were included in the safety and efficacy analyses. Final determination of response was to be made by an IRRP.

5.2.2. Patient Disposition (CLO-222)

Of the 35 patients in CLO-222, the most frequent reason (13 of 35, 37%) patients discontinued treatment with clofarabine was for failure to achieve response after 2 cycles. The second most frequent reason for discontinuation was the patient was scheduled to receive transplant, 9 patients (25.7%). This was followed by death due to AE (5 patients, 14.3%), then investigator decision, AE or treatment toxicity, and disease progression, which occurred in 2 patients each (5.7%).

5.2.3. Patient Demographics (CLO-222)

The median age of patients treated in CLO-222 was 12, with the highest percentage (45.7%) of patients occurring in the 2 to 12 year-old age group. The 16 to 22 (28.6%) and 12 to 16 (20.0%) age groups were the next most heavily represented, with the fewest patients occurring in the 0 to 2 year-old group, only 2 patients (5.7%). There were more males than females by 2 to 1, and the majority of patients were Caucasian. See Table 22.

Table 22: Demographics at Baseline (CLO-222)

		ITT Patients (N=35)
Age (yrs):	N	35
	Mean	11.8
	Median	12
	Standard Deviation	6.18
	Minimum	2
	Maximum	22
Age Category (yrs):	0 to ≤2	2 (5.7%)
	>2 to ≤12	16 (45.7%)
	>12 to ≤16	7 (20.0%)
	>16 to ≤22	10 (28.6%)
Gender:	Female	13 (37.1%)
	Male	22 (62.9%)
Ethnicity:	Hispanic	7 (20.0%)
	Other	3 (8.6%)
	Caucasian	19 (54.3%)
	Black	3 (8.6%)
	Asian	3 (8.6%)

5.2.4. Other Baseline Characteristics (CLO-222)

5.2.4.1. Prior Induction Therapies (CLO-222)

Five patients underwent only 1 prior induction regimen and the majority of patients, 12 patients (34.3%) underwent 2 prior induction regimens. Patients in this study had to have received at least 1 prior induction therapies, and 6 patients (17.1%) received 5 prior to enrollment. The median number of prior induction regimens was 3. See Table 23.

Table 23: Prior Induction Therapies (CLO-222)

	ITT Patients (N=35)	
Number of Prior Induction Regimens	**n**	**%**
1	5	14.3
2	12	34.3
3	8	22.9
4	4	11.4
5	6	17.1

5.2.4.2. Prior Transplants (CLO-222)

Over half of the patients (18/35, 51.4%) in this study had received at least 1 transplant prior to clofarabine treatment, and 5/35 patients (14.3%) had received 2 prior transplants. See Table 24.

Table 24: Prior Transplants (CLO-222)

Number of Prior Transplants	ITT Patients (N=35)	
	n	%
0	17	48.6
1	13	37.1
2	5	14.3

5.2.4.3. Refractory Patients (CLO-222)

Refractory patients were those who either failed their most recent, non-palliative therapeutic regimen or their response was deemed not evaluable. Twenty-two of the 35 patients (62.9%) in CLO-222 were considered refractory. These 22 patients had undergone from 2 to 5 prior regimens.

5.2.5. Extent of Exposure (CLO-222)

Patients in this study received from 1 to 5 cycles of clofarabine treatment, with most patients receiving 1 or 2 cycles of clofarabine. See Table 25.

Table 25: Exposure to Study Drug by Cycle (CLO-222)

Total Number of Cycles Received	ITT Patients (N=35)	
	n	%
1	15	42.9
2	13	37.1
3	4	11.4
4	2	5.7
5	1	2.9

5.2.6. Efficacy Results (CLO-222)

Confirmation of diagnosis was obtained from an independent pathologist with expertise in hematologic malignancies. In addition, an IRRP was used in this trial. The IRRP was comprised of 3 pediatric oncologists who were otherwise not participants in the study; their role was to confirm the response for each patient. Confirmation of response was based on a review of the patient's bone marrow aspirate reports and peripheral blood counts.

5.2.6.1. Efficacy Parameters (CLO-222)

The efficacy parameters in CLO-222 were identical to those in CLO-212 (Section 5.1.6.1). Of particular importance in CLO-222 is the issue of patients who achieved a PR with an M1 marrow. Although patients with an M2 marrow and patients with an M1 marrow can both qualify as a PR, there is a qualitative difference between these two types of PRs. A patient who is a PR by definition but has an M1 marrow could potentially achieve a response of CRp or CR if given time for count recovery. This type of PR may be more indicative of efficacy than patients who are a PR but have an M2 bone marrow.

Patients were assessed for disease response by analysis of their bone marrow aspirate/biopsy prior to each cycle for the first 6 cycles. After Cycle 6, biopsies or aspirates were performed every other cycle. Patients were evaluated for efficacy according to the following definitions.

- Complete remission (CR): Patients who have no evidence of circulating blasts or extramedullary disease; an M1 bone marrow; and recovery of peripheral counts.
- Complete remission in the absence of total platelet recovery (CRp): Patients who have met all criteria for CR except for recovery of platelet counts.
- Partial remission (PR): Patients who have a complete disappearance of circulating blasts; an M2 bone marrow; and appearance of normal progenitor cells; an M1 marrow that does not qualify for CR or CRp.

Response Criteria for Patients with ALL (CLO-222)

Response Category	Response Criteria
CR	• No evidence of circulating blasts or extramedullary disease • M1 bone marrow (<5% blasts) • Recovery of peripheral counts (platelets ≥100 × 10^9/L and ANC ≥1.0 × 10^9/L)
CRp	• Meets all of the criteria for a CR except platelet recovery to ≥100 × 10^9/L
PR	• Complete disappearance of circulating blasts • M2 bone marrow (≥5% and ≤25% blasts) and appearance of normal progenitor cells • M1 marrow that does not qualify for CR or CRp
Treatment failures	• All other responses

Included in the analyses of these 2 pivotal studies, ILEX considered PR an efficacy endpoint for the reasons discussed below. Although reinduction therapies can induce CRs, chemotherapy treatments in refractory patients can also result in a PR that is associated with clinical benefit in acute pediatric leukemias based on the ability of some patients with PR to benefit from subsequent transplant. It should be noted that 2 types of PRs were observed in this study: (1) patients with an M1 marrow but without full recovery of ANC, and (2) patients with an M2 marrow regardless of ANC recovery.

5.2.6.2. The Importance of Partial Remissions in Patients with AML (CLO-222)

It is a more common clinical practice to take AML patients to transplant while in a PR than patients with ALL.[2,10,22] This is particularly true when a patient is a PR due to the lack of full ANC recovery but would otherwise be a CR by response criteria. Modern-day practice patterns in the management of high-risk (multiply relapsed or refractory patients) pediatric acute leukemia populations include proceeding to transplant almost immediately after the last cycle of chemotherapy when a donor is available, without waiting for ANC recovery. This management paradigm is applicable to patients that are at high risk of relapse—such as those patients enrolled in CLO-212 and CLO-222—who had relapsed following several prior induction regimens or who were refractory to the most recent regimen. Investigators participating in these pivotal Phase II studies recommended patients who achieved a PR, or

even "non-responding" patients (according to the IRRP) who had substantial cytoreduction, proceed to transplant without allowing time for complete hematologic recovery or additional cycles of clofarabine.

However, even patients who have not achieved complete clearance of bone marrow blasts, but have substantial reduction in tumor burden may also benefit from transplant. The relative tumor burden of leukemic lymphoblasts has been shown to be a predictor of relapse after chemotherapy and BMT.[62,63,64,65,66] Uckun, et al[63] showed that patients with high counts of leukemic progenitor cells in their bone marrow had a substantially greater risk of relapse after autologous BMT than patients with lower levels of marrow leukemic progenitor cells. From this it is apparent that even though a patient is not a CR, there is still the possibility of a positive outcome if the tumor burden can be lowered prior to transplant.[22]

In a study of pediatric and adult patients with ALL or AML, Sierra et al[22] demonstrated that the relative percent blasts in the bone marrow before allogenic transplant from an HLA-matched donor could be directly correlated with the cumulative incidence of relapse and overall survival. Patients with >30% leukemic blasts in the marrow before starting the conditioning regimen for BMT had a higher risk of relapse and shorter time for leukemia-free survival after transplant than did patients in relapse with <30% blasts in the marrow. The therapeutic goal of lowering the tumor burden, as evidenced by cytoreduction of blasts to a CR or PR state, is therefore meaningful and remains important in both initial chemotherapy and in remission-induction treatments.[22,62,67,68] This speaks to the benefit of new chemotherapies, such as clofarabine, that can induce a CR or PR in relapsed patients who are refractory to prior therapy.

5.2.6.3. Objective Response Rates (CLO-222)

According to the IRRP, no patients achieved a CR, 1 patient (3%) achieved a CRp, and 8 patients (22.9%) achieved a PR. The OR rate (CR+CRp) was 3% (95% CI: 0% to 15%), and 9 patients (25.7%) achieved at least a PR (95% CI: 12% to 43%). The investigators' assessment of response differed from the IRRP's. Both assessments are provided in Table 26 below.

Table 26: Best Objective Response (CLO-222, All Patients)

	ITT Patients (N=35)			
	Investigator Assessment		Independent Panel Assessment	
Response Category	**N**	**%**	**N**	**%**
Complete Remission (CR)	1	3	0	0.0
Complete Remission w/o Total Platelet Recovery (CRp)	1	3	1	3
Partial Remission (PR)	12	34.3	8	22.9
Treatment Failure	16	45.7	19	54.3
Not Evaluable	2	5.7	7	20.0
Not Assessed	3	8.6	0	0.0
Overall Remission (CR + CRp)	2	5.7	1	3
Any Remission (CR + CRp + PR)	14	40.0	9	25.7

95% Confidence Interval for IRRP Rate of Overall Remission (CR + CRp): (0.00, 0.15).
95% Confidence Interval for IRRP Rate of Any Remission (CR + CRp + PR): (0.12, 0.43).

ILEX has used the IRRP's response assessments throughout the clofarabine NDA. However, some patients who did not meet the strict criteria of the IRRP did receive benefit from treatment with clofarabine. For example, a 21-year-old male with M0 AML achieved a CR according to the investigator. The IRRP confirmed this response but determined the patient was not evaluable because he had <25% blasts at study entry and the inclusion criteria specified that patients have ≥25% blasts at study entry. This patient received 2 cycles of 52 mg/m^2/day clofarabine, then a 3rd cycle at 26 mg/m^2/day, and a 4th cycle at 15 mg/m^2/day. At study entry he had 12% blasts, after cycle 1 he had 3% blasts, 2% blasts after cycle 2, 4% blasts after cycle 3, and only 1% blasts after cycle 4. This patient also had a chloroma that resolved after treatment with clofarabine. Approximately 2 months after completing treatment with clofarabine he underwent a transplant. As of data cutoff he had not progressed, his post-transplant survival was 0+ weeks as he underwent the transplant immediately before study cutoff, and his overall survival was 23.3+ weeks. In addition, an 11-year-old female patient was assessed as "not evaluable" by the IRRP but a PR by the investigator. She received 2 cycles of 52 mg/m^2/day clofarabine. She had 20% blasts at study entry, reduced to 8% at end of study and 2% at follow up. She proceeded to transplant

50 days after completing clofarabine treatment and has survived 64.4+ weeks post transplant with an overall survival of 75.3+ weeks.

5.2.6.4. Duration of Remission (CLO-222)

The duration of remission was calculated from the IRRP-determined start of response to first objective evidence of relapse or death, including continued remission for those patients who proceeded to transplant. The duration of remission for the 1 patient who achieved a CRp was 73.4+ weeks.[1] The median duration of remission for patients who achieved at least a PR was 16.2 weeks (95% CI: 1.7 to 73.4+ weeks). See Table 27.

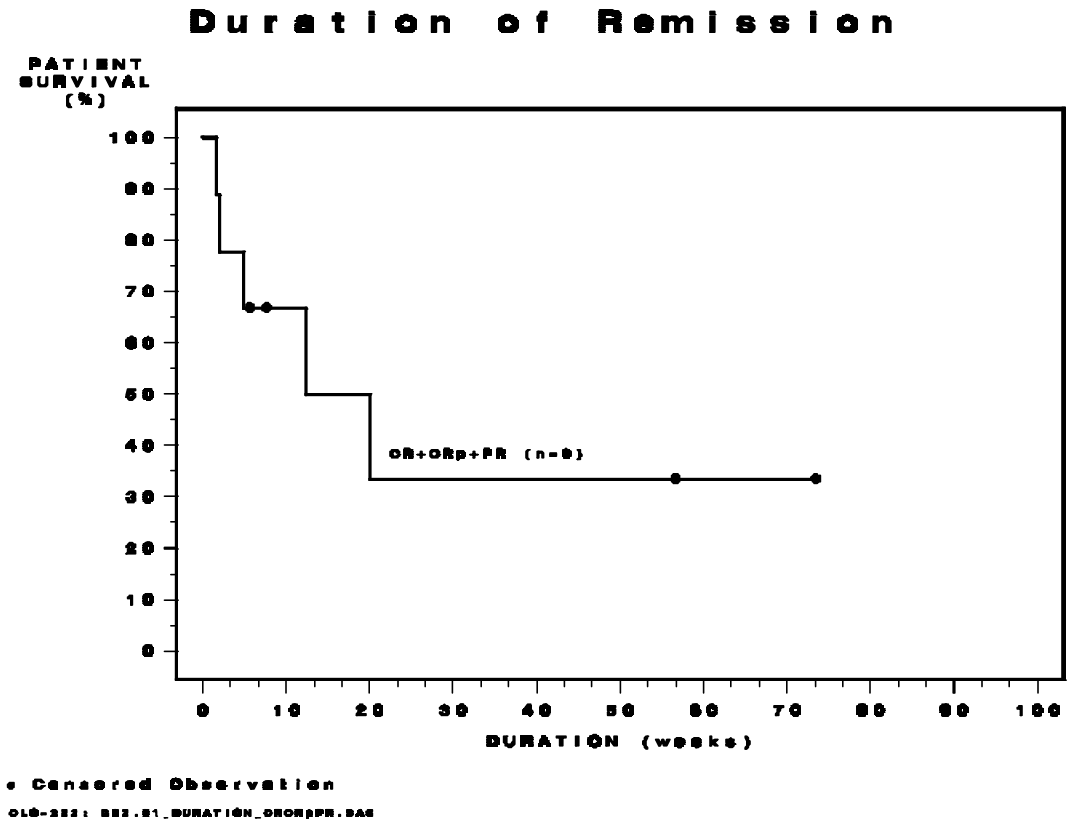
Table 27: Duration of Remission (Weeks) for Patients with AML (CLO-222)

Response Category (IRRP)	N	Kaplan-Meier Median	Lower Limit of 95% CI	Upper Limit of 95% CI	Minimum	Maximum	% Censored[1]
Complete Remission w/o Platelet Recovery (CRp)	1	.	.	.	73.4+	73.4+	100.0
Partial Remission (PR)	8	12.4	2.0	.	1.7	56.6	37.5
Overall Remission (CR + CRp)	1	.	.	.	73.4+	73.4+	100.0
Complete or Partial Remission (CR + CRp + PR)	9	16.2	4.9	.	1.7	73.4+	44.4

[1] Percentage of patients still in remission at data cutoff

[1] In the 120-day update, the duration of remission for this patient was incorrectly identified as 39.9+ weeks; however, ILEX subsequently reassessed duration of remission based on follow-up bone marrow (09 Jan 2004), and determined it to be 73.4+ weeks.

The Kaplan-Meier duration of remission curve for CLO-222 is presented below for patients who achieved at least a PR.



5.2.6.5. Survival (CLO-222)

Survival was calculated from date of first dose of clofarabine to death or last follow up. The 1 patient who achieved a CRp was still alive at 93.6+ weeks. For patients who achieved at least a PR the median survival was 39.0 weeks (95% CI: 24.3 weeks to upper limit not estimated). See Table 28. The Kaplan-Meier curves for CLO-222 survival are presented in the Executive Summary.

Table 28: Survival (Weeks) for Patients with AML (CLO-222)

Response Category (IRRP)	N	Kaplan-Meier Median	Lower Limit of 95% CI	Upper Limit of 95% CI	Minimum	Maximum	% Censored[1]
Complete Remission w/o Platelet Recovery (CRp)	1	.	.	.	93.6	93.6	100.0
Partial Remission (PR)	8	30.3	24.30	.	7.7	67.9	50.0
Treatment Failure/Not Evaluable (TF + NE)	26	12.4	5.40	22.10	1.6	84.9	15.4
Overall Remission (CR + CRp)	1	.	.	.	93.6	93.6	100.0
Complete or Partial Remission (CR + CRp + PR)	9	39.0	24.30	.	7.7	93.6	55.6
All Patients	35	21.0	7.70	30.30	1.6	93.6	25.7

[1] Percentage of patients still alive at data cutoff

5.2.6.6. Post-Treatment Transplant (CLO-222)

In this study, 12/35 patients (34.3%) went on to receive a transplant after clofarabine treatment. Patient ages ranged from 2 to 22 and they received from 1 to 5 cycles of clofarabine. Time to transplant after clofarabine treatment ranged from 21 days to 75 days, indicating that these patients proceeded to transplant very quickly. Seven of the 12 patients who proceeded to transplant were still alive at data cutoff. Their survival post transplant ranged from 0+ weeks to 64.4+ weeks. It is noteworthy that of these 12 patients, the IRRP determined that 1 had achieved a CRp and 6 had achieved a PR, representing fully 75% of all patients who achieved at least a PR in this study. In addition, the IRRP assessed 3 patients as not evaluable and 2 patients as treatment failures. See Table 29.

Table 29: Patients Who Proceeded to Bone Marrow or Stem Cell Transplant (CLO-222)

Sex (Age)	# of Cycles of Clofarabine	Determination of Response IRRP/ Investigator (PR marrow type & % blasts at transplant)	Days to Transplant Post-Clofarabine[1]	Initial Post-Transplant Bone Marrow	Alive (Y/N)	Survival from Start of Clofarabine[2] (weeks)	Survival Post-Transplant[3] (weeks)
Male (21)	4	NE/CR	75	NA	Yes	23.3+	0.0+
Male (4)	5	CRp/CRp	53	2% blasts normocellular	Yes	93.6+	63.4+
Male (5)	3	PR/PR (M2 marrow 6% blasts)	48	1% blasts normocellular	Yes	16.4+	1.1+
Male (15)	2	PR/PR (M1 marrow 0% blasts)	38	1% blasts hypocellular	No	30.3	21.3
Female (22)	2	PR/PR (M1 marrow 5% blasts)	25	2% blasts hypocellular	No	39.0	32.7
Male[4] (3)	4	PR/PR (28% blasts)	21	3% blasts hypocellular	Yes	29.0+	16.4+
Female (4)	2	PR/PR (M1 marrow 4% blasts)	39	1% blasts normocellular	Yes	24.9+	15.9+
Male (11)	1	PR/PR (M2 marrow 13% blasts)	65	1% blasts	Yes	67.9+	58.0+
Male (17)	1	NE/NE	37	0% blasts normocellular	No	24.4	18.7
Female (11)	2	NE/PR (M2 marrow 8% blasts)	50	2% blasts normocellular	Yes	75.3+	64.4+
Male (18)	2	TF/PR (M1 marrow 2% blasts)	23	0% blasts	No	28.7	22.3
Male (2)	1	TF/NE	30	1% blasts hypercellular	No	38.0	33.1

[1] Time from the date of last dose of clofarabine to date of transplant.
[2] Time from the date of first dose of clofarabine to death or last follow-up.
[3] Time from the date of transplant to death or last follow-up.
[4] Because of an increase in blast count after this patient's response and before he went to transplant, the investigator administered another cycle of clofarabine and the patient, with an aplastic marrow, proceeded immediately to transplant.

The population of patients who went on to transplant helps illustrate the clinical benefit of the PR response in patients with AML. For example, a 5-year-old male patient had

undergone 2 transplants prior to treatment with clofarabine. In addition, he had undergone 1 regimen of chemotherapy prior to his first transplant and a second regimen after his second transplant. He received 3 cycles of 52 mg/m^2/day clofarabine. At study entry he had 59% blasts, after cycle 3 he had 6% blasts, and at follow up after his post-clofarabine transplant he had 1% blasts. At data cutoff he was still in remission, his post-transplant survival was 1.1+ weeks, and his overall survival was 16.4+ weeks. An 11-year-old male patient, also assessed as a PR by the IRRP, entered the study with 52% blasts, which decreased to 0% after cycle 1. Two months after completing Cycle 1, he proceeded to transplant, with 1% blasts after transplant. At data cutoff he was still in remission with post-transplant survival of 58.0+ weeks and overall survival of 67.9+ weeks.

Patients who were assessed as "not evaluable" by the IRRP also demonstrated clinical benefit from clofarabine treatment. See Section 5.2.6.3 for a discussion of selected patients who received clinical benefit from treatment with clofarabine.

5.2.6.7. Refractory Patients (CLO-222)

Twenty-two of the 35 patients (62.9%) in this study were refractory to their most recent prior chemotherapy. Of these 22 patients, 4 (18.2%) achieved a PR and 4 were not evaluable. It is also worth noting that 3 of the 4 refractory patients assessed as PR proceeded to transplant, as did a refractory patient assessed as treatment failure by the IRRP but PR by the investigator. See Table 30.

Table 30: Best Objective Response for Refractory Patients (CLO-222)

(Response to Last Prior Chemotherapy was Either Treatment Failure or Not Evaluable)				
	N=22			
	Investigator Assessment		Independent Panel Assessment	
Response Category	**n**	**%**	**n**	**%**
Complete Remission (CR)	0	0.0	0	0.0
Complete Remission w/o Total Platelet Recovery (CRp)	0	0.0	0	0.0
Partial Remission (PR)	6	27.3	4	18.2
Treatment Failure	11	50.0	14	63.6
Not Evaluable	2	9.1	4	18.2
Not Assessed	3	13.6	0	0.0
Overall Remission (CR + CRp)	0	0.0	0	0.0
Any Remission (CR + CRp + PR)	6	27.3	4	18.2

95% Confidence Interval for IRRP Response Rate of Any Remission (CR + CRp + PR): (0.05, 0.40).

The number and variety of prior regimens these patients had received is worth noting. Most of these patients had undergone several prior multi-drug chemotherapeutic regimens. Table 31 below presents the prior regimen information for some patients as well as their response to clofarabine treatment. It should be noted that 2 of these patients were refractory to prior treatment with other nucleoside analogues, ie, fludarabine or cladribine.

Table 31: Refractory Patients' Prior Regimens and Response to Clofarabine (CLO-222)

PT ID	IRRP/Response/ Investigator Response	Number of Prior Regimens	Most Recent Prior Regimen (Number of Cycles)	Clofarabine Dose/ (Number of Cycles)
10-year-old Male	PR/PR	4	mitoxantrone and cytarabine (1 cycle) dexamethasone, 6-mercaptopurine (1 cycle)	52 mg/m^2/day (3)
5-year-old Male[1]	PR/PR	3	Zarnestra (2 cycles)	52 mg/m^2/day (3)
15-year-old Male[1]	PR/PR	5	AMLREZBFM97	52 mg/m^2/day (2)
11-year-old Male	PR/PR	2	idarubicin and cladribine (1 cycle)	52 mg/m^2/day (1)
14-year-old Male	TF/PR	2	fludarabine, cytarabine, idarubicin (1 cycle)	52 mg/m^2/day (3)

[1] indicates patients who received a transplant prior to treatment with clofarabine

The median duration of remission for refractory patients who achieved a PR was 20.0 weeks (95% CI: 1.7 weeks to upper limit not estimated). See Table 32.

Table 32: Duration of Remission (weeks) for Refractory Patients with AML (CLO-222)

(Response to Last Prior Chemotherapy Either Treatment Failure or Not Evaluable) N=22							
Response Category (IRRP)	**N**	**Kaplan-Meier Median**	**Lower Limit of 95% CI**	**Upper Limit of 95% CI**	**Minimum**	**Maximum**	**% Censored[1]**
Partial Remission	4	20.0	1.7	.	1.7	56.6	50.0
Complete or Partial Remission (CR+CRp+PR)	4	20.0	1.7	.	1.7	56.6	50.0

[1] Percentage of patients still alive at data cutoff

5.2.6.8. Patients with a Prior Transplant (CLO-222)

Of the 18 patients in this study who had undergone a prior transplant, 1 achieved a CRp and 3 achieved a PR. The OR rate was 5.6% and the response rate was 22.2% for patients who achieved at least a PR. Median duration of remission for patients who achieved a PR was 16.2 weeks (95% CI: 12.4 to 20.0 weeks). For patients who achieved at least a PR, median duration of remission was 20.0 weeks (95% CI: 12.4 weeks to upper limit not estimated). See Table 33.

Table 33: Duration of Remission (weeks) for Patients with a Prior Transplant (CLO-222)

Response Category (IRRP)	**N**	**Kaplan-Meier Median**	**Lower Limit of 95% CI**	**Upper Limit of 95% CI**	**Minimum**	**Maximum**	**% Censored[1]**
Partial Remission	3	16.2	12.4	20.0	5.6	20.0	33.3
Complete or Partial Remission (CR+CRp+PR)	4	20.0	12.4	.	5.6	73.4+	50.0

[1] Percentage of patients still alive at data cutoff

5.2.7. Efficacy Conclusions (CLO-222)

Patients with AML who were enrolled in the Phase II study of clofarabine had also developed highly resistant disease by the time of study entry. In many cases the patients had become refractory to standard agents or approaches such as myeloablative stem cell transplant. More than half of the patients enrolled in this study had undergone prior stem cell transplantation and nearly two-thirds had become refractory to standard therapeutic attempts at remission induction. As with the patients with ALL, the responses that were observed provided for durable disease control and also allowed selected patients with an available donor to proceed to transplant. However, it should be noted that only 1 CRp was observed, and this patient underwent a stem cell transplant after 5 cycles of clofarabine and has survived for 63+ weeks after transplant. Before treatment with clofarabine, this patient had been in remission for approximately 35 weeks following his most recent induction remission and stem cell transplant.

There were other patients who achieved a PR with substantial reduction or cleared their marrow of disease and were taken off study to proceed to transplant. In several instances the patient went rapidly to transplant before recovery of peripheral blood counts. This approach resulted in several patients achieving a PR (M1 marrow, but without meeting the CR criteria of having an ANC of >1000). The clinical approach of taking patients off study for transplant was observed early in the study because it was felt by investigators that it was in the best interest of the patients to proceed to transplant without waiting for peripheral count recovery or undergoing additional cycles of clofarabine. To illustrate this approach, there are the basic treatment details of an 11-year-old male patient with M4 AML who failed to respond to cladribine and idarubicin (POG9720) before entering the clofarabine study. He received 1 cycle of clofarabine, which reduced his bone marrow blasts from 52% at study entry to 0%. He went off study with an increasing ANC and no peripheral blasts to undergo a cord blood MUD transplant. While this patient was considered a PR by study criteria, he has remained in remission for 57+ weeks following clofarabine and transplant.

These data demonstrate that clofarabine provides clinical benefit in patients with highly resistant AML. The approach taken by many of the investigators to proceed to transplant

under suboptimal conditions (ie, PR or substantial cytoreduction) highlights the aggressiveness of this disease and the need for additional agents such as clofarabine.

5.2.8. Safety Results (CLO-222)

Safety results for both CLO-212 and CLO-222 are included in the integrated safety assessment in Section 6.

5.3. Combined Efficacy Results

The primary analysis of efficacy for this submission focused on the data from ILEX's 2 pivotal Phase II trials: CLO-212 in patients with ALL (49 patients) and CLO-222 in patients with AML (35 patients) for a combined total of 84 patients. In addition, efficacy was assessed in the Phase I dose-escalation trial, ID99-383 (25 patients, 17 with ALL and 8 with AML), for a total of 66 pediatric patients with ALL and 43 pediatric patients with AML having undergone single-agent treatment with clofarabine.

The OR rate of 20% and the PR rate of 10% in CLO-212 successfully confirmed and expanded the results in the pediatric Phase I/II study (ID99-383). Although the 3% OR rate seen with CLO-222 was lower than the 20% OR rate seen in the CLO-212 study, the rate might have been higher if not for the practice pattern of taking patients to transplant before they had ANC recovery that was required for achieving a CR. Because so many of the patients with AML had no other curative treatment options, there was little or no likelihood that they could have proceeded to transplant without undergoing treatment with clofarabine because of the refractory nature of their disease and the attendant tumor burden. In addition, pediatric AML is inherently a more resistant type of leukemia than ALL. The 23% PR rate in the CLO-222 study was higher than the 10% in the CLO-212 study, which again may reflect taking patients to transplant prior to ANC recovery. The percent of patients with at least a PR (CR, CRp, and PR) was comparable between the 2 ILEX studies, 31% for CLO-212 compared to 26% for CLO-222.

ILEX does not contend that ALL and AML are the same diseases. However, to show how many total patients benefited from treatment with single-agent clofarabine, we have

combined the responses from CLO-212 and CLO-222. For the 2 pivotal Phase II studies, a combined total of 6 patients achieved a CR, 5 patients achieved a CRp, and 13 patients achieved a PR.

A total of 20 patients from the 2 studies proceeded to transplant, although a patient in CLO-212 was not in remission at the time of transplant and is not included in the clinical benefit analysis. In the Phase I dose-escalation study, ID99-383, an additional 7 patients proceeded to transplant after treatment with single-agent clofarabine. Thus, a total of 26 patients received clinical benefit from clofarabine and proceeded to transplant. Table 34 presents the number of patients from each of the pivotal Phase II studies and the Phase I study who proceeded to transplant after single-agent treatment with clofarabine, and the IRRP determination of response to clofarabine.

Table 34: Patients Who Proceeded to Transplant and their Response to Clofarabine

IRRP Determination of Response to Clofarabine	Number of Patients from CLO-212	Number of Patients from CLO-222	Number of Patients with ALL from ID99-383	Number of Patients with AML from ID99-383	Total Number of Patients Who Proceeded to Transplant Post Clofarabine
CR	2	0	2	0	4
CRp	2	1	0	0	3
PR	2	6	2	0	10
NE	1	3	0	0	4
TF	0	2	0	0	2
No IRRP review	0	0	1	2	3
Total	**7**	**12**	**5**	**2**	**26**

NB: 1 additional patient from CO-212 proceeded to transplant; however, this patient was a treatment failure and was not in remission. This patient is not included in the patients who received clinical benefit from treatment with clofarabine.

In addition to the 4 patients in ID99-383 with ALL whose response was confirmed by the IRRP, 3 more patients from this study proceeded to transplant. Two of the patients had AML and had an investigator determination of response as PR and “improvement” and 1 patient had ALL and an investigator determination of response as “improvement.”

Durable remission (ie, ≥8 weeks) was achieved by an additional 3 patients from CLO-212. These were patients who did not proceed to transplant. Two of these patients with a durable remission had a response of CR and 1 had a response of CRp, all from CLO-212. Thus a combined total of 29 patients from these 3 studies, CLO-212, CLO-222, and ID99-383, received clinical benefit from single-agent treatment with clofarabine by proceeding to transplant or sustaining durable remission.

Karnofsky Performance Status (KPS) was followed for the 2 pivotal Phase II studies. KPS scores remained the same or improved for the majority of patients with ALL in CLO-212 (52.4%). KPS scores stayed the same or improved for 71.4% of the patients with AML in CLO-222. Considering the condition of these patients and the fact that they were undergoing yet another chemotherapy regimen, it is noteworthy that more than half of all these patients had KPS values that stayed the same or improved.

The bulleted list below summarizes the key efficacy variables by study for the patients in CLO-212 and CLO-222, plus a summary of response data for the patients in the Phase I dose-escalation trial (ID99-383).

- In the Phase I dose-escalation trial (ID99-383), 4/17 patients with ALL (23.5%) achieved a CR, 1 patient with ALL (5.8%) achieved a response of PR, for a response rate of 29.4% in patients with ALL who achieved at least a PR. In this same trial, 1/8 patients with AML (12.5%) achieved a response of CR, 2 patients with AML (25%) achieved a response of PR, for a response rate of 37.5% in patients with AML who achieved at least a PR. The IRRP determined that according to the Phase II response criteria, the 5 investigator-assessed CRs were 2 CRs, 1 CRp, and 2 PRs.
- The OR rate (CR + CRp) for patients with ALL (CLO-212) was 20% (6 CR, 4 CRp; 95% CI: 10% to 34%); the response rate for patients achieving at least a PR (CR + CRp + PR) was 31% (95% CI: 18% to 45%).
- The OR rate (CR + CRp) for patients with AML (CLO-222) was 3% (0 CR, 1 CRp; 95% CI: 0% to 15%)), although there were other clinical benefits achieved, such as substantial cytoreduction allowing patients to proceed to transplant. The response rate for patients who achieved at least a PR (CR + CRp + PR) was 26% (95% CI: 12% to 43%). In addition, 1 patient in this study had a response that the IRRP confirmed as a CR; however, they classified the response as not evaluable because the patient only had 12% blasts at study enrollment. That patient also had a chloroma with 100% blasts that resolved following treatment with clofarabine.

- The OR rate (CR + CRp) for patients with ALL (CLO-212) who were refractory to the most recent prior therapy was 17% (3 CR, 2 CRp); the response rate in this population for patients achieving at least a PR (CR + CRp + PR) was 23%. Thirty of the 49 patients (61%) in this study were refractory to their most recent prior regimen. Of the 7 refractory patients who responded to treatment with clofarabine, the median number of prior regimens was 4. Included in these patients' most recent prior regimens were such chemotherapeutic agents as ifosfamide, carboplatin, cytarabine, idarubicin, vincristine, cyclophosphamide, high-dose methotrexate, and 6-thioguanaine. See Table 19 in Section 5.1.6.6.

- The OR rate (CR + CRp) for patients with AML (CLO-222) who were refractory to the most recent prior therapy was 0%; the response rate in this subpopulation for patients achieving at least a PR (CR + CRp + PR) was 18%. Twenty-two of the 35 patients (63%) in this study were refractory to their most recent prior regimen. Of the 4 refractory patients who responded to treatment with clofarabine, the median number of prior regimens was 3. Included in these patients' most recent prior regimens were such chemotherapeutic agents as mitoxantrone, cytarabine, dexamethasone, 6-mercaptopurine, zarnestra, idarubicin, cladribine, fludarabine and the multi-drug regimen called AMLREZBFM97. See Table 31 in Section 5.2.6.7.

- The median duration of remission for patients with ALL (CLO-212) who achieved an OR (CR + CRp) was 20.2 weeks. The median duration of remission for patients with ALL who achieved at least a PR (CR + CRp + PR) was 9.7 weeks.

- The duration of remission for the 1 patient with AML (CLO-222) who achieved a CRp was 73.4+ weeks. The median duration of remission for patients with AML who achieved at least a PR (CR + CRp + PR) was 16.2 weeks.

- The median duration of remission for patients with ALL (CLO-212) who were refractory to the most recent prior therapy who achieved an OR (CR + CRp) was 6.1 weeks. The median duration of remission in this subpopulation for patients with ALL achieving at least a PR (CR + CRp + PR) was 4.6 weeks.

- The median duration of remission for patients with AML (CLO-222) who were refractory to the most recent prior therapy who achieved at least a PR (CR + CRp + PR) was 20.0 weeks.

- The median survival for patients with ALL (CLO-212) who achieved an OR had not yet been reached as 7 of the 10 patients with ALL were still alive at data cutoff. The median survival for patients with ALL who achieved at least a PR (CR + CRp + PR) was 42.0 weeks.

- The survival for the 1 patient with AML (CLO-222) who achieved a CRp was 93.6+ weeks. The median survival for patients with AML who achieved at least a PR (CR + CRp + PR) was 39.0 weeks.

- In CLO-212, CLO-222, and ID99-383 combined, 26 patients received clinical benefit from clofarabine and proceeded to transplant. Of these patients, 12/66 had ALL and 14/43 had AML.

- In CLO-212, CLO-222, and ID99-383 combined, 29/109 patients benefited from single-agent treatment with clofarabine either through proceeding to transplant or sustaining a durable remission. Of these patients, 15/66 had ALL and 14/43 had AML.

The efficacy results for the 2 ILEX studies (CLO-212 and CLO-222) are displayed in Table 35. The exposure to clofarabine was similar between the 2 studies as was the distribution of patients by demographic factors (age and sex).

Table 35: Summary of Efficacy Variables for Pediatric ALL and AML

Efficacy Variable	CLO-212 (ALL) (N=49)	CLO-222 (AML) (N=35)
Exposure		
Median cumulative dose	540 mg	540 mg
Range of doses	29 to 1905 mg	140 to 1560 mg
Median cycles	2	2
Range of cycles	1 to 8	1 to 5
Number of Cycles		
1	21 (42.9%)	15/35 (43%)
2	19 (38.8%)	13/35 (37%)
3 or more	9 (18.4%)	7/35 (20%)
Number of Patients who Received Drug	49	35
Males	29 (59.2%)	22 (62.9%)
Females	20 (40.8%)	13 (37.1%)
Patient Ages		
Median (years)	12.0	12.0
Range	1 to 20	2 to 22
Overall Remission	10 (20.4%)	1 (3%)
CR	6 (12.2%)	0 (0%)
CRp	4 (8.2%)	1 (3%)
Number (%) of Patients with PR	5 (10.2%)	8/35 (23%)
Number (%) of Patients with at Least PR	15 (30.6%)	9/35 (26%)
Median Duration of Remission		
Patients with at least PR	9.7 weeks	16.2 weeks
Patients with CR	median not yet reached	----
Patients with CRp	20.2 weeks	remission 73.4+ weeks
Patients with OR	20.2 weeks	----
Patients with PR	2.7 weeks	12.4 weeks
Response in Patients Refractory to Last Multi-agent Regimen	n=30	n=22
CR	3/30 (10%)	----
CRp	2/30 (7%)	----
OR (CR + CRp)	5/30 (17%)	----
Patients with at least PR	7/30 (23%)	4/22 (18%)

Table 35: Summary of Efficacy Variables for Pediatric ALL and AML (continued)

Efficacy Variable	CLO-212 (ALL) N=49	CLO-222 (AML) N=35
Median Duration of Remission in Refractory Patients	n=30	n=22
CR	n=3, 6.1 weeks	----
CRp	n=2, median not yet reached	---
PR	n=2, 2.5 weeks	n=4, 20.0 weeks
OR (CR + CRp)	n=5, 6.1 weeks	----
Patients with at least PR	n=7, 4.6 weeks	n=4, 20.0 weeks
Median Time for Survival		
All patients	11.7 weeks	21.0 weeks
Patients with at least PR	42.0 weeks	39.0 weeks
Patients with CR	5 of 6 alive (10.4+ to 44.0+ weeks)	----
Patients with CRp	2 of 4 alive (28.3+ to 63.1+ weeks)	1 alive at 93.6+ weeks
Patients with OR	7 of 10 alive (10.4+ to 63.1+ weeks)	----
Patients with PR	29.7 weeks	30.3 weeks
Clinical Benefit		
Transplant (HSCT)	7 (14.3%)	12 (34%)
Durable remission (≥8 weeks) in patients who did not go to transplant	3/41 (7.3%)	0/23 (0%)
Best On-Study Karnofsky scores	n=42	n=28
Improved	9 (21%)	6 (21%)
Stayed the Same	13 (31%)	14 (50%)
Worsened	20 (48%)	8 (29%)
Not assessed	7	7

CR=complete remission, CRp=complete remission without platelet recovery, OR=overall remission, PR=partial remission, HSCT=hematopoietic stem cell transplant

5.4. Overall Efficacy Conclusions

In summary, these Phase II pivotal studies combined with the data from the Phase I study, have shown the clinical benefit of clofarabine in obtaining remissions in this multiply relapsed, resistant population, or substantial cytoreduction that allowed patients to proceed to transplant. The combined response rate for patients in the Phase II studies (24/84, 28.6%) who achieved at least a PR is impressive, particularly considering the extent of prior

treatments, and the number of concurrent illnesses and concomitant medications in this highly refractory population. The combined response rate for patients in the Phase II studies who were refractory to their most recent prior regimen (11/52, 21.2%) and who achieved at least a PR is equally impressive, particularly when combined with the 5 patients from ID99-383 who, according to the investigator, achieved a CR (4 with ALL and 1 with AML) and the 3 patients from that study who, according to the investigator, achieved a PR (1 with ALL, 2 with AML). It should be noted that the IRRP review of the 5 investigator-assessed CRs using the Phase II criteria resulted in 2 CRs, 1 CRp, and 2 PRs. The population studied in the pivotal Phase II trials had a large number of concurrent illnesses that can cause dose interruption, delay, or early discontinuation, in addition to being treated with numerous concomitant medications that can affect organ function and result in decreased dose intensity. The Phase II trials have demonstrated that single-agent treatment with clofarabine can effectively treat patients with these challenges.

The pediatric leukemia patients in these 2 studies achieved IRRP-confirmed response (CR, CRp, and PR) with durable remission of up to 56.6+ weeks (with transplant, CLO-222) and up to 24.4+ (without transplant, CLO-212). A total of 20/84 (24%) clofarabine-treated patients with acceptable donors proceeded to transplant with prolonged survival (63.1+ weeks in CLO-212 and up to 93.6+ weeks in CLO-222), including patients who did not meet the response criteria but were still sent to transplant (up to 32.4+ weeks in CLO-212 and up to 75.3+ weeks in CLO-222). The dose of 52 mg/m^2 administered daily for 5 days resulted in an OR rate of 13% (11/84) between both studies. The proportion of patients who achieved at least a PR in both studies was 29% (24/84). The median survival for patients who had at least a PR was 42.0 weeks and 39.0 weeks, respectively, for ALL (CLO-212) and AML (CLO-222) patients.

Clofarabine at the 52 mg/m^2/day dose $\times$ 5 is indicated for use in pediatric patients with refractory or relapsed acute leukemias. This is a population with an unmet medical need as many of these patients are severely ill and have no viable therapeutic options. Clofarabine has demonstrated evidence of efficacy in relapsed or refractory pediatric patients with acute leukemias, resulting in documented, independently confirmed objective responses, according

to modified COG criteria. Clofarabine's impressive cytoreduction has enabled patients to proceed to transplant when they otherwise might not have had the opportunity. A number of additional patients, especially those with AML in CLO-222, might have achieved a CR or CRp had sufficient time been allowed for count recovery. In these cases, patients were discontinued from the study while in PR, or even as non-responders according to the IRRP, to enable them to go on to transplant.

Clofarabine has been able to produce a beneficial response in patients when all other treatment options have failed. There are no directly comparable studies in the Phase II setting, as published reports of investigational regimens are typically in patients that are less heavily pretreated than in ILEX's pivotal Phase II studies and do not represent the modern-day population, use differing criteria for response, are of very small size, or have not used an IRRP to objectively confirm response.

Clofarabine responses have included durable remissions and the opportunity to proceed to transplant, which offers the only reasonable possibility of long-term survival for this population.

6. INTEGRATED SAFETY RESULTS

The integrated safety database was developed from several studies: DM93-036 (2 pediatric patients), CLO-141 (1 pediatric patient), CLO-212 (49 pediatric patients), CLO-222 (35 pediatric patients), ID99-383 (25 pediatric patients), and CLO-221 (1 pediatric patient).

MDACC conducted 2 Phase I studies and 2 Phase II studies with clofarabine in adult and pediatric patients with leukemias and solid tumors. In addition, ILEX has conducted a total of 5 clinical studies with clofarabine in patients with leukemias and solid tumors as well as an emergency expanded access program. Table 1 in Section 1.2.2, provides a chronology of the clofarabine studies including the study sponsor, the population, and the indication along with the EEAP.

This section provides the safety results for the 113 pediatric patients in the integrated database who received at least 1 infusion of clofarabine. These 113 pediatric patients were comprised of 67 patients diagnosed with ALL and 46 patients diagnosed with AML. With rare exceptions, the type, frequency, and severity of AEs were similar between patients with ALL and patients with AML. The majority of patients in the integrated database (84 of 113 patients) participated in the 2 ILEX pivotal trials in this application (CLO-212, N=49 ALL or CLO-222, N=35 AML). The remainder came from DM96-036 (2 pediatric patients, ID99-383 (25 pediatric patients), CLO-141 (1 pediatric patient), and CLO-221 (1 pediatric patient). Most patients were male, Caucasian or Hispanic, and between the ages of 2 and 12 years (median age 12 years).

6.1. Disposition, Demographics and Baseline Characteristics

Results for disposition, demography, and exposure are summarized in Section 6.1.1, Section 6.1.2, and Section 6.2, respectively. The results are presented in an integrated fashion by disease type (ALL or AML) for the 113 pediatric patients in the integrated safety population (25 patients from ID99-383, 49 patients from CLO-212, 35 patients from CLO-222, and 4 pediatric patients from the adult studies). Results for efficacy are provided

in Section 5.1.6 and Section 5.2.6, respectively, for the 84 patients enrolled in CLO-212 and CLO-222.

6.1.1. Patient Disposition

The end-of-study disposition for the 113 pediatric patients in the integrated safety database is presented in Table 36. The most frequent reason for study discontinuation was lack of efficacy (either failure to achieve response after 2 cycles or disease progression) (51% overall; 55% ALL, 46% AML). A total of 14% (16/113) of patients overall (13% ALL, 15% AML) were removed from a study due to death, and 4% overall (3% ALL, 4% AML) discontinued a trial due to a non-fatal AE. (Deaths and discontinuations due to AEs are discussed in greater detail in Section 6.3.3 and its subsections.)

Table 36: End of Study Disposition for Pediatric Patients

	ALL (N=67)		AML (N=46)		ALL/AML (N=113)	
End of Study Disposition Category	**n**	**%**	**N**	**%**	**n**	**%**
Withdrawn from study total	65	97.0	45	97.8	110	97.3
Lack of efficacy:	37	55.2	21	45.7	58	51.3
Failure to achieve response after 2 cycles	21	31.3	14	30.4	35	31.0
Disease progression	16	23.9	7	15.2	23	20.4
Scheduled to receive transplant:	9	13.4	10	21.7	19	16.8
Death:	9	13.4	7	15.2	16	14.2
Due to adverse event	5	7.5	6	13.0	11	9.7
Due to malignant disease	1	1.5	1	2.2	2	1.8
Due to other reason	3	4.5	0	0.0	3	2.7
Non-fatal adverse event	2	3.0	2	4.3	4	3.5
Other reason:	8	11.9	5	10.9	13	11.5
Investigator decision	3	4.5	3	6.5	6	5.3
Refused further treatment	4	6.0	2	4.3	6	5.3
Other	1	1.5	0	0.0	1	0.9
On study at data cut-off	2	3.0	1	2.2	3	2.7

6.1.2. Demographic and Baseline Disease Characteristics

The age, sex, ethnicity, and baseline disease of the 113 pediatric patients in the integrated safety population are presented in Table 37. The integrated safety population is used for

demographics, disposition, exposure to clofarabine, baseline disease characteristics, and all safety analyses and discussions. (In contrast, the efficacy population is comprised of the 84 patients in the pivotal Phase II trials, 49 patients with ALL and 35 patients with AML.)

Overall, the integrated safety population was predominantly male with a median age of 12 years (range 1 to 22 years). Most patients were either Caucasian or Hispanic. More specifically, the pediatric patients treated at 52 mg/m^2/day (n=96) were 59% male, 49% Caucasian and 31% Hispanic, with a median age of 12 years (range 1 to 22 years).

Table 37: Demographic Characteristics of Pediatric Patients Exposed to Clofarabine

Demographic Characteristic	Category	ALL (N=67)		AML (N=46)		ALL/AML (N=113)	
		N	%	n	%	n	%
Age category	0 to ≤2	3	4.5	5	10.9	8	7.1
	>2 to ≤12	32	47.8	19	41.3	51	45.1
	>12 to ≤16	15	22.4	8	17.4	23	20.4
	>16 to ≤22	17	25.4	14	30.4	31	27.4
Age (years)	N	67	.	46	.	113	.
	Mean	12.18	.	11.67	.	11.97	.
	STD	4.96	.	6.45	.	5.59	.
	Median	12.00	.	12.00	.	12.00	.
	Minimum	1	.	1	.	1	.
	Maximum	20	.	22	.	22	.
Sex	Male	40	59.7	28	60.9	68	60.2
	Female	27	40.3	18	39.1	45	39.8
Ethnicity	Caucasian	29	43.3	24	52.2	53	46.9
	Hispanic	28	41.8	10	21.7	38	33.6
	Black	6	9.0	5	10.9	11	9.7
	Asian	.	.	4	8.7	4	3.5
	Other	4	6.0	3	6.5	7	6.2

6.1.3. Previous Therapy for Acute Leukemia

Although a total of 89% (101/113) of pediatric patients overall (93% ALL, 85% AML) had from 1 to 4 induction regimens prior to treatment with clofarabine, only 10% of pediatric patients overall (3% ALL, 20% AML) had a maximum of 1 prior induction regimen. Thirty-four percent overall (33% ALL, 35% AML) had 2 prior induction regimens, 26% overall

(30% ALL, 20% AML) had 3 prior induction regimens, and 20% overall (27% ALL, 11% AML) had 4 prior induction regimens. The median number of prior regimens for ALL was 3 and for AML was 2. In the combined ALL/AML safety population, the combined median number of prior regimens was 3. In the pivotal Phase II trials, 30/49 (61.2%) of patients with ALL (CLO-212) were refractory to their most recent prior regimen and 22/35 (62.9%) of patients with AML (CLO-222) were refractory to their most recent prior regimen. The following is a partial list of chemotherapeutic agents to which the patients in CLO-212 and CLO-222 were refractory: L-asparaginase, gleevec, hydroxyurea, vincristine, cytarabine, doxorubicin, ifosfamide, carboplatin, daunomycin, idarubicin, PEG-asparaginase, mitoxantrone, etoposide, 6-thioguanine, mylotarg, temozolomide, interleukin-2, zarnestra, cladribine, and fludarabine. Most of the refractory patients received several drugs in combination. For a discussion of these patients' response to treatment with clofarabine and for additional detail on prior regimens see Section 5.1.6.6 (ALL) and Section 5.2.6.7 (AML).

6.2. Patient Exposure to Clofarabine

The proposed dosing regimen and duration of treatment for clofarabine are outlined in Section 1.7. The majority of pediatric patients (85%, 96/113) received a maximum daily dose of clofarabine 52 mg/m^2. Fourteen patients overall (7 ALL, 7 AML) received a maximum daily dose of clofarabine less than 52 mg/m^2 (ie, a maximum daily dose ranging from 11.25 mg/m^2 to 40 mg/m^2). Three patients received a maximum daily dose greater than 52 mg/m^2 (1 AML patient received 56 mg/m^2/day, and 2 ALL patients received 70 mg/m^2/day). Most of the pediatric patients (60% overall; 64% ALL, 54% AML) received at least 2 cycles of treatment with clofarabine.

The 113 pediatric patients in the integrated safety database were exposed to clofarabine in 6 clinical trials; there were 67 patients diagnosed with ALL and 46 patients diagnosed with AML. Table 38 presents the number of pediatric patients exposed to clofarabine by age category. Most pediatric patients were >2 to ≤12 years of age.

Table 38: Number of Patients Exposed to Clofarabine by Indication and Age Category

Age Category	ALL (N=67) N	AML (N=46) n	ALL/AML (N=113) N
0 to ≤2	3	5	8
>2 to ≤12	32	19	51
>12 to ≤16	15	8	23
>16 to ≤22	17	14	31
Total	67	46	113

6.3. Safety Results

6.3.1. Overview of Safety Events

Table 39 presents an overview of the on-study safety events regardless of causality (ie, those events reported during treatment and up to 30 days after administration of the last dose) that occurred in the integrated safety database. It is worth noting that a large number of adverse effects were already present in many of the patients at baseline. In fact, 98% of the patients in the 2 pivotal Phase II studies had at least 1 concurrent condition at baseline. The most frequent pre-existing conditions included alopecia, tachycardia, fatigue, pyrexia, nausea, anorexia, and vomiting, each of which was present in at least 20% of the patients at baseline. The most common on-study toxicities, regardless of causality, that were observed during exposure to clofarabine were gastrointestinal system AEs, including vomiting, nausea, and diarrhea; adverse hematologic effects, including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile neutropenia; and infection.

A total of 83% of pediatric patients experienced at least 1 serious adverse event (SAE). (It should be noted that drug-related SAEs—as determined by the investigator—were reported in 59%, 67/113 of pediatric patients overall; 55%, 37/67 ALL and 65%, 30/46 AML). Four pediatric patients permanently discontinued treatment with clofarabine due to an AE. Laboratory abnormalities were not assessed for relationship to clofarabine unless reported as an AE. It should be noted that it is likely that the majority of pediatric patients entered the

studies with red blood cell- and/or platelet transfusion-dependency. The fact that the hematologic status of this safety population was already compromised should be considered in the interpretation of the hematologic toxicity data. As patients proceeded to receive more cycles of clofarabine, there was some indication toward dose reduction at ≥3 cycles (2/9, 22%, in patients with ALL and 2/7, 29%, in patients with AML).

Table 39: Summary of On-Study Safety Events, Regardless of Causality

Safety Event:	Patients with ALL (N=67)	Patients with AML (N=46)	Integrated Safety Database Total (N=113)
Deaths	16 (24%)	10 (22%)	26 (23%)
Any Serious Adverse Event	51 (76%)	43 (93%)	94 (83%)
Any Adverse Event ≥ Grade 3	63 (94%)	45 (98%)	108 (96%)
Discontinuation due to Adverse Events	2 (3%)	2 (4%)	4 (4%)

Safety aspects of special interest for this population include infections, hepato-biliary effects, renal effects, capillary leak syndrome and SIRS, and cardiovascular effects. These issues are discussed in Section 6.3.5 and its subsections.

Metabolic abnormalities were common and not unexpected in this heavily pretreated patient population. This likely reflects poor nutritional status, toxicities from prior therapies, the use of concurrent medications such as amphotericin B and cyclosporine, as well as the development of tumor lysis, diarrhea, nausea, and vomiting. Metabolic toxicities during treatment with clofarabine included changes in potassium (hypokalemia), sodium (hypo and hypernatremia), glucose (hyperglycemia and hypoglycemia), calcium (hypercalcemia and hypocalcemia), magnesium (hypermagnesemia and hypomagnesemia), albumin (hypoalbuminemia), phosphorus (hypophosphatemia), uric acid (hyperuricemia), and carbon dioxide (decreased CO_2). The most common of these included hyperglycemia (in 66% of patients overall) and hypocalcemia (in 58% of patients overall), followed by hypoalbuminemia (in 42% of patients overall), hypophosphatemia (in 37% of patients overall), and hypomagnesemia (in 29% of patients overall). In general, most of the observed post-baseline toxicities were grade 1 or grade 2.

6.3.2. All Adverse Events Reported On-Study

There were rare differences in AEs between patients with ALL and patients with AML; otherwise AEs were similar for all pediatric patients treated with single-agent clofarabine. Although not included in our NDA, a comparison of patients treated earlier in the pivotal Phase II trials with those patients treated more recently, appears to demonstrate a trend of diminishing SAEs.

More generally, AEs that occurred in ≥15% of pediatric patients overall, regardless of causality, are presented by NCI CTC toxicity grade in Table 40 below. The most commonly reported events of grade 3 or 4 severity were febrile neutropenia (grade 3, 54%; grade 4, 4%), nausea (grade 3, 15%; grade 4, 1%), pyrexia (grade 3, 15%; grade 4, 0%), and epistaxis (grade 3, 14%; grade 4, 0%).

Table 40: Adverse Events in ³ 15% of Pediatric Patients Overall by NCI CTC Toxicity Grade, Regardless of Causality

	ALL/AML (N=113)											
	Total		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
Preferred Term[1]	n	%	n	%	N	%	n	%	n	%	n	%
Total patients with adverse events	112	99.1	.	.	4	3.5	60	53.1	26	23.0	22	19.5
Vomiting NOS	94	83.2	24	21.2	59	52.2	10	8.8	1	0.9	.	.
Nausea	82	72.6	10	8.8	54	47.8	17	15.0	1	0.9	.	.
Febrile neutropenia	67	59.3	.	.	1	0.9	61	54.0	5	4.4	.	.
Diarrhoea NOS	59	52.2	31	27.4	17	15.0	11	9.7	.	.	.	.
Headache NOS	54	47.8	25	22.1	23	20.4	6	5.3	.	.	.	.
Pruritus NOS	54	47.8	21	18.6	32	28.3	1	0.9	.	.	.	.
Pyrexia	45	39.8	11	9.7	17	15.0	17	15.0	.	.	.	.
Dermatitis NOS	43	38.1	15	13.3	21	18.6	7	6.2	.	.	.	.
Fatigue	42	37.2	22	19.5	16	14.2	3	2.7	1	0.9	.	.
Rigors	42	37.2	25	22.1	14	12.4	3	2.7	.	.	.	.
Abdominal pain NOS	41	36.3	19	16.8	14	12.4	8	7.1	.	.	.	.
Tachycardia NOS	36	31.9	19	16.8	11	9.7	6	5.3	.	.	.	.
Anorexia	34	30.1	11	9.7	11	9.7	5	4.4	7	6.2	.	.
Petechiae	34	30.1	17	15.0	10	8.8	7	6.2	.	.	.	.
Epistaxis	33	29.2	16	14.2	1	0.9	16	14.2	.	.	.	.
Pain in limb	33	29.2	12	10.6	15	13.3	6	5.3	.	.	.	.
Hypotension NOS	31	27.4	2	1.8	9	8.0	12	10.6	8	7.1	.	.
Anxiety NEC	26	23.0	10	8.8	14	12.4	2	1.8	.	.	.	.
Cough	25	22.1	20	17.7	5	4.4	.	.	.	.	.	.
Constipation	24	21.2	11	9.7	13	11.5	.	.	.	.	.	.
Erythema NEC	21	18.6	16	14.2	5	4.4	.	.	.	.	.	.
Mucosal inflammation NOS	21	18.6	10	8.8	8	7.1	3	2.7	.	.	.	.
Pain NOS	20	17.7	3	2.7	9	8.0	7	6.2	1	0.9	.	.
Flushing	19	16.8	19	16.8	.	.	.	.	.	.	.	.
Oedema NOS	19	16.8	3	2.7	13	11.5	1	0.9	2	1.8	.	.
Haematuria	17	15.0	11	9.7	4	3.5	2	1.8	.	.	.	.

[1] Patients with more than one occurrence of the same preferred term are counted only once.

6.3.3. Deaths, Serious Adverse Events and Other Significant Adverse Events

6.3.3.1. Deaths

A total of 23% (26/113) of pediatric patients exposed to clofarabine died on-study or within 30 days of the last dose of clofarabine. The incidence of death in the clofarabine safety

population does not appear substantially different from what has been previously reported, even when compared to some studies that were conducted in less heavily pretreated patients with ALL or AML. Harris et al[69] reported on a Phase II study conducted by the Children's Cancer Group with high-dose cytarabine and L-asparaginase in patients with ALL in first relapse who failed attempts to achieve a second CR. In that study, out of 52 patients there were 17 bacterial infections (3 fatal), 17 invasive fungal infections (12 fatal), and 1 fatal adenoviral infection. In the first 28 days post-high dose cytarabine and L-asparaginase, 19% died from either progressive leukemia (4 patients) or from infections or toxicity (6 patients). Leahey et al,[21] reported on a Phase I/II study (0922) conducted by the Children's Cancer Group with fludarabine, idarubicin, and cytarabine in patients with AML who had failed prior therapies. It is noteworthy that the patients who were treated in this study had failed only 1 prior regimen. In the first 30 days after treatment, 20% of the patients died, including 1 from respiratory distress and hepatotoxicity.

During the clofarabine pediatric development program, 26 patients (16 ALL, 10 AML) died on-study or within 30 days of the last dose of clofarabine. None of these patients died during or on the same day as the clofarabine infusion. These deaths are listed in Table 41. This table is sorted by cause of death and indication, and the data are **bolded** for the patients whose deaths were considered related to study drug.

There was no clustering in terms of time to death post-dosing. Two of the deaths occurred the day after the last dose of clofarabine, an additional 5 deaths occurred within 2 days of the last dose, 4 deaths occurred within 1 week after the last dose of clofarabine, 13 occurred within 25 days after the last dose, and the remaining 2 occurred more than 25 days after the last dose of clofarabine, including 1 patient who died 38 days after clofarabine dosing. Thus, 11 deaths occurred within a week of the patient's last dose of clofarabine, 13 deaths within 25 days after last dose, and 2 deaths beyond 25 days. Most of the patients who died (25 of 26 received at least one full cycle of clofarabine 52 mg/m^2/day, and >45% patients were treated for either 1 cycle (12 patients) or 2 full or partial cycles (12 patients). Two patients received 3 cycles of treatment.

Twelve patients died from progressive disease, 5 of whom also experienced at least one AE that contributed to death (ie, at least one grade 5 AE): a patient from ID99-383 (multi-organ failure), a patient from CLO-212 (hepatic disorder NOS and renal impairment NOS), a patient from CLO-222 (septic shock), a patient from CLO-212 (sepsis NOS), and a patient from CLO-222 (progressive AML).

Four of the deaths were considered by the investigator to be related to treatment with clofarabine: 1) 1 patient with ALL from CLO-212 died from drug-related acute vascular leak syndrome that contributed to cardiac arrest; 2) another patient with ALL from CLO-212 died from drug-related respiratory failure and liver damage; 3) a third patient with ALL from CLO-212 died from drug-related multi-organ failure; and 4) a patient with AML from CLO-222 died from drug-related septic shock and multi-organ failure.

Table 41: Listing of Deaths On-Study or Within 30 Days of the Last Dose of Clofarabine

Study No.	Indication	Age	Sex	Ethnicity	Dose	No. Cycles	Cause of Death[a]	Grade 5 AEs	Days to Death[b]
Deaths Due to Disease Progression[a]									
ID99-383	ALL	12	Male	Hispanic	11.5	2	Malignant disease	None	16
ID99-383	ALL	7	Female	Hispanic	30	Cycle 1 & 1 dose of Cycle 2	Malignant disease	Multi-organ failure	25
CLO-212	ALL	14	Male	Caucasian	52	2	Disease progression	Hepatic disorder NOS, Renal impairment NOS	1
CLO-212	ALL	9	Male	Hispanic	52	2	Progressive disease	None	2
CLO-212	ALL	19	Female	Caucasian	52	1	Malignant disease	Sepsis NOS	2
CLO-212	ALL	17	Female	Caucasian	52	Cycle 1, & 3 doses of Cycle 2	Progressive disease	None	25
CLO-212	ALL	13	Female	Caucasian	52	1	Progressive disease	Disease progression	23
CLO-222	AML	11	Female	Caucasian	52	1	Progressive disease	Progressive disease	19
CLO-222	AML	2	Female	Hispanic	52	1	Progressive disease	Progressive leukemia	22
CLO-222	AML	17	Male	Caucasian	52	1	Malignant disease	Progressive AML	25
CLO-222	AML	3	Female	Asian	52	1	Malignant disease	None	30
CLO-222	AML	15	Male	Pakistani	52	1	Septic shock related to E. coli infection, malignant disease	Septic shock	7

Table 41: Listing of Deaths On-Study or Within 30 Days of the Last Dose of Clofarabine (continued)

Patient No.	Indication	Age	Sex	Ethnicity	Dose	No. Cycles	Cause of Death[a]	Grade 5 AEs	Days to Death[b]
Deaths Due to Other Causes[a]									
ID99-383	ALL	5	Female	Caucasian	52	2	Pulmonary hemorrhage	Pulmonary hemorrhage	5
ID99-383	ALL	15	Male	Hispanic	52	2	Sepsis NOS	Sepsis NOS	2
ID99-383	AML	5	Female	Caucasian	52	1	Renal failure NOS	Renal failure NOS	6
CLO-212[c]	ALL	15	Male	Hispanic	52	2	Multi-organ failure	Multi-organ failure	12
CLO-212	**ALL**	**12**	**Male**	**Hispanic**	**52**	**2**	**Acute vascular leak syndrome (related); & hypotension, pulmonary edema, & cardiac arrest (not related)**	**Cardiac arrest**	**2**
CLO-212[c]	**ALL**	**17**	**Male**	**Caucasian**	**52**	**4 doses of Cycle 1**	**Respiratory failure, liver damage**	**Respiratory distress, Hepatocellular damage**	**13**
CLO-212	ALL	15	Female	Arabic	52	2	Sepsis, worsening pneumonia, increased creatinine	Sepsis NOS, Pneumonia NOS	21
CLO-212	ALL	9	Female	Caucasian	52	1	Multi-organ failure	Multi-organ failure	3
CLO-212	**ALL**	**20**	**Male**	**Hispanic**	**52**	**2**	**Hand foot syndrome, multi-organ failure**	**Multi-organ failure**	**21**
CLO-212	ALL	7	Female	Hispanic	52	1	Multi-organ failure	Multi-organ failure	38
CLO-222	AML	18	Male	Caucasian	52	3	Septic shock, pulmonary hemorrhage	Xanthomas sepsis, Pulmonary hemorrhage	15
CLO-222	AML	10	Male	Hispanic	52	3	Septic shock	Septic shock	2

Table 41: Listing of Deaths On-Study or Within 30 Days of the Last Dose of Clofarabine (continued)

Patient No.	Indication	Age	Sex	Ethnicity	Dose	No. Cycles	Cause of Death[a]	Grade 5 AEs	Days to Death[b]
Deaths Due to Other Causes[a] (continued)									
CLO-222	**AML**	**20**	**Female**	**Caucasian**	**52**	**Cycle 1 & 3 doses Cycle 2**	**Septic shock, multi-organ failure**	**Septic shock, Multi-organ failure**	**1**
CLO-222	AML	13	Female	Black	52	1	Cardiopulmonary arrest	Cardio-respiratory arrest	23

Note: Patients whose deaths were considered by the investigator to be related to clofarabine treatment are in **bold** font.
[a] Cause of death as reported in the patient narrative.
[b] Days from date of last dose of clofarabine to date of death.
[c] Autopsy was performed and additional autopsy data are available from ILEX upon request.

6.3.3.2. Serious Adverse Events

For the purposes of regulated clinical trials, SAEs are defined as any adverse drug experience that occurs at any dose that results in any of the following outcomes:

- Death.
- Life-threatening adverse drug experience.
- Requires inpatient hospitalization or prolongation of existing hospitalization. For the purposes of CLO-212 and CLO-222, hospitalizations for protocol-scheduled procedures, blood product transfusions, or social reasons (ie, awaiting transport home) were not to be considered SAEs.
- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- Requires medical or surgical intervention to prevent one of the outcomes listed above.

Serious adverse events are recorded and reported to the regulatory authorities regardless of duration, outcome, or relationship to study drug.

During the previous 12-month period, ILEX solicited two expert reviews of the SAEs in the pivotal Phase II trials. In November 2003, a group of 3 pediatric oncologists, Sima Jeha, Peter Steinherz, and Craig Hurwitz, reviewed the SAEs for patterns of unusual or unacceptable toxicities. In March 2004, these 3 conducted a second review, joined by another pediatric oncologist, Mark Bernstein, and a pediatric cardiologist, Laurel Steinherz. Following both reviews, the basic conclusion was that the pattern of toxicities was as expected in this population of patients.

A total of 83% of pediatric patients overall (76% ALL, 94% AML) experienced at least 1 SAE. The majority of these SAEs were hospitalizations and/or life-threatening conditions, which were not unexpected in this study population. Most (91 of 94 events) were grade 3 or higher according to the NCI CTC, with 23% (22/94) of the patients having at least 1 SAE that contributed to death.

Table 42 presents the SAEs that occurred in more than 2 pediatric patients overall by preferred term and severity grade regardless of the investigator's determination of causality.

Serious adverse events occurring in at least 10% of patients overall included febrile neutropenia (46% ALL, 57% AML), pyrexia (10% ALL, 13% AML), hypotension NOS (9% ALL, 15% AML), and sepsis NOS (13% ALL, 13% AML).

Table 42: Serious Adverse Events in 2 or More Pediatric Patients Overall by NCI CTC Grade

	ALL/AML (N=113)											
	Total		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
Preferred Term[1]	n	%	n	%	N	%	n	%	n	%	n	%
Total patients with serious adverse events	94	83.2	.	.	3	2.7	50	44.2	19	16.8	22	19.5
Febrile neutropenia	57	50.4	.	.	1	0.9	53	46.9	3	2.7	.	.
Sepsis NOS	15	13.3	.	.	.	.	7	6.2	3	2.7	5	4.4
Hypotension NOS	13	11.5	.	.	1	0.9	7	6.2	5	4.4	.	.
Pyrexia	13	11.5	2	1.8	5	4.4	6	5.3	.	.	.	.
Neutropenia	10	8.8	.	.	.	.	3	2.7	7	6.2	.	.
Nausea	9	8.0	.	.	2	1.8	7	6.2	.	.	.	.
Septic shock	9	8.0	.	.	.	.	1	0.9	5	4.4	3	2.7
Vomiting NOS	9	8.0	1	0.9	2	1.8	6	5.3	.	.	.	.
Bacteraemia	7	6.2	.	.	.	.	7	6.2	.	.	.	.
Pneumonia NOS	7	6.2	1	0.9	.	.	4	3.5	1	0.9	1	0.9
Staphylococcal bacteraemia	7	6.2	.	.	.	.	6	5.3	1	0.9	.	.
Multi-organ failure	6	5.3	.	.	.	.	.	.	.	.	6	5.3
Respiratory distress	6	5.3	.	.	.	.	3	2.7	2	1.8	1	0.9
Staphylococcal infection NOS	6	5.3	.	.	.	.	6	5.3	.	.	.	.
Cellulitis	4	3.5	.	.	.	.	4	3.5	.	.	.	.
Herpes simplex	4	3.5	.	.	2	1.8	2	1.8	.	.	.	.
Herpes zoster	4	3.5	.	.	1	0.9	3	2.7	.	.	.	.
Capillary leak syndrome	3	2.7	.	.	.	.	1	0.9	2	1.8	.	.
Diarrhoea NOS	3	2.7	.	.	1	0.9	2	1.8	.	.	.	.
Disseminated intravascular coagulation	3	2.7	.	.	.	.	2	1.8	1	0.9	.	.
Hyperbilirubinaemia	3	2.7	.	.	.	.	.	.	3	2.7	.	.
Infection NOS	3	2.7	.	.	.	.	2	1.8	1	0.9	.	.
Proctalgia	3	2.7	.	.	1	0.9	2	1.8	.	.	.	.
Renal failure NOS	3	2.7	.	.	.	.	1	0.9	1	0.9	1	0.9
Tumour lysis syndrome	3	2.7	.	.	.	.	3	2.7	.	.	.	.
Abdominal pain NOS	2	1.8	.	.	.	.	2	1.8	.	.	.	.
Alanine aminotransferase increased	2	1.8	.	.	.	.	2	1.8	.	.	.	.
Aspartate aminotransferase increased	2	1.8	.	.	.	.	2	1.8	.	.	.	.

Table 42: Serious Adverse Events in 2 or More Pediatric Patients Overall by NCI CTC Grade (continued)

	ALL/AML (N=113)											
	Total		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
Preferred Term[1]	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Colitis pseudomembranous	2	1.8	.	.	.	.	2	1.8	.	.	.	.
Dehydration	2	1.8	.	.	1	0.9	1	0.9	.	.	.	.
Disease progression NOS	2	1.8	.	.	.	.	.	.	.	.	2	1.8
Dyspnoea NOS	2	1.8	.	.	.	.	.	.	2	1.8	.	.
Fungal infection NOS	2	1.8	.	.	.	.	1	0.9	1	0.9	.	.
Headache NOS	2	1.8	.	.	.	.	2	1.8	.	.	.	.
Hypersensitivity NOS	2	1.8	.	.	.	.	2	1.8	.	.	.	.
Influenza	2	1.8	.	.	.	.	2	1.8	.	.	.	.
Pleural effusion	2	1.8	1	0.9	.	.	.	.	1	0.9	.	.
Pneumonia fungal NOS	2	1.8	.	.	.	.	1	0.9	1	0.9	.	.
Pulmonary haemorrhage	2	1.8	.	.	.	.	.	.	.	.	2	1.8
Renal impairment NOS	2	1.8	.	.	2	1.8	.	.	.	.	.	.
Respiratory failure (exc neonatal)	2	1.8	.	.	.	.	.	.	1	0.9	1	0.9
Septicaemia staphylococcal	2	1.8	.	.	.	.	2	1.8	.	.	.	.

[1] Patients with more than one occurrence of the same preferred term are counted only once.

A total of 59% (67/113) pediatric patients overall (55% [37/67] ALL, 65% [30/46] AML) experienced at least 1 SAE considered related to study drug by the investigator. Drug-related SAEs in ALL and AML patients represent 1 patient only unless otherwise noted. They included (according to grade):

- Grade 5: multi-organ failure (2 patients), hepatocellular damage, respiratory distress, and septic shock,
- Grade 4: neutropenia (7 patients), capillary leak syndrome (2 patients), cholecystitis acute NOS, bone marrow depression NOS, cholelithiasis, febrile neutropenia, hyperbilirubinemia (2 patients), overdose NOS, septic shock, maculo-papular rash, hypotension, hyperuricemia, and hypocalcemia;

- Grade 3: febrile neutropenia (32 patients), nausea (4 patients), hypotension (4 patients), tumor lysis syndrome (3 patients), neutropenia (3 patients), ALT increased (2 patients), pyrexia (3 patients), sepsis NOS (3 patients), diarrhea NOS (2 patients), AST increased (2 patients), vomiting NOS (2 patients), capillary leak syndrome, colitis pseudomembranous, convulsions NOS, esophagitis NOS, headache NOS, *Herpes simplex*, *Herpes zoster* (2 patients), hypersensitivity NOS, gastritis NOS, groin infection, ileus, *Legionella* infection NOS, *parainfluenza* virus infection NOS, peripheral motor neuropathy, pneumonia NOS (2 patients), *staphylococcal bacteremia*, tachycardia, bacteremia (2 patients), septicemia staphylococcal, urinary tract infection NOS, staphylococcal infection NOS; gingival bleeding, disseminated intravascular coagulation, serum sickness, blood bilirubin increased, and infection NOS;

- Grade 2: pyrexia (4 patients), nausea (3 patients), vomiting NOS (3 patients), febrile neutropenia (2 patients), dehydration, palmar-plantar erythrodysesthesia syndrome, cholestasis, increased blood iron, agitation, depressed level of consciousness, dystonia, somnolence, and dysarthria; and

- Grade 1: pyrexia (3 patients), and erythema not elsewhere classified (NEC).

6.3.3.3. Discontinuations and Dose Delays Due to Adverse Events

The end of study disposition for the 113 pediatric patients in the integrated database was presented earlier in Section 6.1.1. The most frequent reason for study discontinuation was lack of efficacy (either failure to achieve response after 2 cycles or disease progression) (51% overall; 55% ALL, 46% AML). A total of 14% (16/113) of patients overall (13% ALL, 15% AML) were removed from a study due to death, and 4% overall (3% ALL, 4% AML) discontinued a trial due to a non-fatal AE. See Table 43.

Table 43: Listing of Discontinuations Due to Adverse Events for Pediatric Patients Overall

Indication	Study Number	Age (yr)	Sex	Dose Cohort	MedDRA Version 3.3 Preferred Term	Case Report Form Term	Onset Date	NCI Grade	Relation of AE to Study Drug	Days Since First Dose[a]	Days Since Last Dose[b]
ALL	CLO-212	18	Female	52 mg/m²	Hyperbilirubinaemia	Hyperbilirubinemia	06JAN2003	4	Related to study drug	70	13
ALL	ID99-383	17	Male	>52 mg/m²	Hyperbilirubinaemia	Hyperbilirubinemia	08DEC2001	4	Related to study drug	5	1
AML	CLO-222	13	Female	52 mg/m²	Ventricular arrhythmia NOS	Ventricular arrhythmia	30JUL2003	4	Other	9	5
AML	CLO-222	11	Female	52 mg/m²	Disease progression NOS	Progressive disease	09SEP2002	5	Related to cancer	20	16

[a] Time from the date of first dose of clofarabine to the onset date of AE.
[b] Time from the date of last dose of clofarabine to the onset date of AE.

Overall, the AEs that contributed to dose delays, interruptions, and modifications included drug-related grade 3 agitation, feeling abnormal, hypersensitivity NOS, rash maculo-papular, and vomiting NOS; drug-related grade 2 anxiety NEC, depressed level of consciousness, dystonia, headache NOS, muscle twitching, vomiting NOS. A patient with AML in CLO-222 developed septic shock after the fourth dose of Cycle 3, and died the following day (before the fifth dose of Cycle 3). In addition, 3 patients had dose delays due to grade 3 septicemia staphylococcal (ALL patient from ID99-383), grade 3 hypotension NOS (ALL patient from CLO-212), or grade 2 pyrexia (AML patient from CLO-222). A patient with AML from ID99-383 had a laboratory toxicity that led to the delay of clofarabine dosing (as well as a reduction of the dose of clofarabine). This patient needed time to recover from grade 3 or 4 neutropenia and thrombocytopenia.

6.3.4. Analysis of Adverse Events by Patient Subgroups

In order to assess whether the reported occurrence rate of AEs differed among different groups of patients, subsets of the integrated safety database were examined.

6.3.4.1. Adverse Events by Treatment Cycle

Table 44 presents the AEs reported by at least 20% of pediatric patients overall according to treatment cycle, for cycles 1 to 8.

Although the total exposure to clofarabine (ie, total mg per patient) increased with each successive cycle, the AE data by cycle show no evidence of cumulative toxicity with clofarabine. The incidence of the individual AEs tended to decrease with each successive cycle, except for the incidence of febrile neutropenia, which remained fairly constant. In contrast, AEs such as diarrhea decreased from 45% in Cycle 1 to 17% in Cycle 3; headache decreased from 37% in Cycle 1 to 17% in Cycle 3; hypotension decreased from 20% in Cycle 1 to 8% in Cycle 3. This could be due to a “first-cycle” effect, possibly due to cytokine release or tumor lysis, which occurs in a more significant manner than in comparison to subsequent cycles. Alternatively, this could be due to patient selection, ie,

only patients who tolerate clofarabine well in the first cycle are likely to proceed to subsequent cycles.

Fever due to neutropenia is an expected consequence of the known pharmacologic activity of clofarabine, as well as the disease of leukemia, so it is not surprising that this AE was reported at a constant level with each cycle of administration.

Table 44: Adverse Events in ³20% of Pediatric Patients Overall by Treatment Cycle

	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8	
Preferred Term[1]	**n**	**%[2]**	**n**	**%[2]**	**n**	**%[2]**	**n**	**%[2]**	**n**	**%[2]**	**n**	**%[2]**	**n**	**%[2]**	**n**	**%[2]**
Total patients exposed per cycle	113	100.0	68	100.0	24	100.0	7	100.0	4	100.0	2	100.0	2	100.0	2	100.0
Vomiting NOS	89	78.8	26	38.2	6	25.0	.	.	.	.	.	.	2	100.0	.	.
Nausea	79	69.9	22	32.4	5	20.8	1	14.3	.	.	.	.	.	.	.	.
Diarrhoea NOS	51	45.1	12	17.6	4	16.7	.	.	.	.	.	.	.	.	.	.
Febrile neutropenia	50	44.2	29	42.6	9	37.5	2	28.6	.	.	1	50.0	1	50.0	1	50.0
Pruritus NOS	48	42.5	6	8.8	.	.	1	14.3	.	.	1	50.0	.	.	.	.
Headache NOS	42	37.2	16	23.5	4	16.7	1	14.3	.	.	.	.	.	.	.	.
Pyrexia	39	34.5	7	10.3	3	12.5	1	14.3	.	.	.	.	.	.	.	.
Abdominal pain NOS	36	31.9	9	13.2	2	8.3	.	.	.	.	.	.	.	.	.	.
Dermatitis NOS	35	31.0	9	13.2	5	20.8	1	14.3	.	.	.	.	.	.	.	.
Rigors	31	27.4	10	14.7	4	16.7	1	14.3	.	.	.	.	.	.	1	50.0
Anorexia	30	26.5	6	8.8	.	.	1	14.3	.	.	.	.	.	.	.	.
Fatigue	29	25.7	13	19.1	2	8.3	.	.	.	.	1	50.0	.	.	.	.
Tachycardia NOS	27	23.9	10	14.7	.	.	1	14.3	.	.	1	50.0	.	.	.	.
Pain in limb	24	21.2	8	11.8	1	4.2	1	14.3	.	.	.	.	.	.	.	.
Epistaxis	23	20.4	7	10.3	4	16.7	1	14.3	.	.	.	.	.	.	.	.
Hypotension NOS	23	20.4	8	11.8	2	8.3	.	.	.	.	.	.	.	.	.	.
Petechiae	23	20.4	9	13.2	.	.	1	14.3	.	.	.	.	.	.	1	50.0

[1] Patients with more than one occurrence of the same preferred term per cycle are counted only once.
[2] Percentage of patients is calculated with the denominator being the total number of patients exposed per cycle.

6.3.4.2. Adverse Events by Demographic Parameter

This section presents the distribution of AEs (regardless of relationship to study drug) according to age, sex, and ethnicity.

AGE

Table 45 presents the distribution of AEs by age category for the AEs reported by at least 20% of pediatric patients overall. Frequently occurring AEs that may indicate increasing incidence with increasing age included nausea, headache NOS, fatigue, tachycardia NOS, hypotension NOS, and constipation. Similarly, pruritus NOS, dermatitis NOS, diarrhea NOS, and cough showed a trend for decreasing incidence with increasing age.

Table 45: Distribution of Adverse Events by Age Category for Adverse Events in ³20% of Pediatric Patients Overall

	ALL/AML (N=113)									
	Total (N=113)		0 to £2 years (N=8)		>2 to £12 years (N=51)		>12 to £16 years (N=23)		>16 to £22 years (N=31)	
MedDRA Version 3.3. Preferred Term	**n**	**%**	**n**	**%**	**N**	**%**	**n**	**%**	**n**	**%**
Total patients with adverse events	112	99.1	8	100.0	51	100.0	23	100.0	30	96.8
Vomiting NOS	94	83.2	5	62.5	45	88.2	19	82.6	25	80.6
Nausea	82	72.6	2	25.0	40	78.4	15	65.2	25	80.6
Febrile neutropenia	67	59.3	3	37.5	35	68.6	13	56.5	16	51.6
Diarrhoea NOS	59	52.2	4	50.0	28	54.9	15	65.2	12	38.7
Headache NOS	54	47.8	2	25.0	23	45.1	11	47.8	18	58.1
Pruritus NOS	54	47.8	4	50.0	29	56.9	9	39.1	12	38.7
Pyrexia	45	39.8	6	75.0	17	33.3	12	52.2	10	32.3
Dermatitis NOS	43	38.1	5	62.5	22	43.1	9	39.1	7	22.6
Fatigue	42	37.2	2	25.0	15	29.4	9	39.1	16	51.6
Rigors	42	37.2	2	25.0	22	43.1	10	43.5	8	25.8
Abdominal pain NOS	41	36.3	2	25.0	24	47.1	7	30.4	8	25.8
Tachycardia NOS	36	31.9	3	37.5	14	27.5	6	26.1	13	41.9
Anorexia	34	30.1	1	12.5	19	37.3	9	39.1	5	16.1
Petechiae	34	30.1	4	50.0	14	27.5	8	34.8	8	25.8
Epistaxis	33	29.2	1	12.5	18	35.3	8	34.8	6	19.4
Pain in limb	33	29.2	2	25.0	22	43.1	4	17.4	5	16.1
Hypotension NOS	31	27.4	.	.	13	25.5	4	17.4	14	45.2
Anxiety NEC	26	23.0	1	12.5	11	21.6	8	34.8	6	19.4
Cough	25	22.1	2	25.0	11	21.6	8	34.8	4	12.9
Constipation	24	21.2	.	.	8	15.7	6	26.1	10	32.3

Notes: Patients with more than one occurrence of the same preferred term are counted only once.

6.3.4.3. Sex

Most of the frequently occurring AEs were reported by similar percentages of male and female patients. This finding is consistent with pharmacokinetic analyses that showed no pharmacokinetic differences between the sexes. The greatest difference in incidence between the 2 sexes was observed for anxiety NEC. The incidence of anxiety NEC for females (28.9%) was 1.5 times the incidence for males (19.1%).

6.3.4.4. Ethnicity

It is difficult to evaluate the data for Black patients, Asian patients, and other ethnic patients, especially the data for each indication, because of the small number of patients in each of these ethnic groups (respectively, N=11, N=4, N=7). Therefore, only differences between Caucasians (N=53) and Hispanics (N=38) will be discussed in this section.

Most of the frequently occurring AEs were reported by similar percentages of Caucasian and Hispanic patients. The greatest differences in incidence between the 2 ethnic groups included increased incidence in Caucasians for fatigue, abdominal pain, and epistaxis.

6.3.5. Safety Aspects of Special Interest

This section presents greater detail on AEs of special interest to the administration of clofarabine, including infections; effects on the hepato-biliary system, effects on the renal system, effects on the cardiovascular system, and SIRS and capillary leak syndrome.

6.3.5.1. Infections

Because of prolonged immunosuppression and myelosuppression from prior therapies and refractory disease, this population is susceptible to a wide range of illnesses, particularly fungal infections or bacterial infections. This section describes the various infections observed during the clofarabine pediatric clinical trials.

A total of 85% of pediatric patients overall (85% ALL, 85% AML) experienced at least one post-baseline infection. Most post-baseline infections (77 of 96 patients reporting) were

grade 3 or greater. Post-baseline infections were considered to be life-threatening or disabling (ie, grade 4 AEs) in 12 of the 96 patients who experienced an infection.

At least one post-baseline infection contributed to the death of 8 pediatric patients overall (3 ALL, 5 AML). Grade 5 infections included sepsis NOS (5% ALL, 4% AML), septic shock (0% ALL, 7% AML), and pneumonia NOS (2% ALL, 0% AML). Only one grade 5 infection was considered by the investigator to be related to treatment with clofarabine; this was an occurrence of septic shock in 1 (3%) AML patient.

Drug-related post-baseline infections occurred in 1 to 3 patients each. The drug-related infections that occurred in only 1 patient each were colitis pseudomembranous, *Escherichia coli* sepsis, groin infection, *Legionella* infection NOS, *parainfluenzae* virus infection NOS, septicaemia *staphylococcal*, and *staphylococcal* bacteraemia (in 1 ALL patient each), and *cytomegalovirus* infection, infection NOS, and sinusitis NOS (in 1 AML patient each). All drug-related infections were grade 3 in severity, with the following exceptions: there was one report each of grade 1 and grade 2 oral *candidiasis* in ALL patients, one report of grade 4 implant infection in an AML patient, one report of grade 4 septic shock in an ALL patient, and 1 report of a grade 5 septic shock in an AML patient.

6.3.5.2. Hepato-Biliary System

The liver is a known target organ of clofarabine toxicity, and hepato-biliary toxicities were frequently observed in pediatric patients during treatment with clofarabine. Therefore, this finding was not unexpected in this heavily pre-treated study population. In addition, many patients had received prior drug therapy (eg, methotrexate) that can result in hepatic toxicities or were also receiving concomitant medications, such as voriconazole, that may have contributed or independently resulted in decreased hepato-biliary function.

Most patients experienced the onset or worsening of elevated AST (75% overall; 74% ALL, 77% AML) or ALT (76% overall; 79% ALL, 70% AML). The incidence of grade 3 or 4 AST shifted from 0% overall at baseline to 38% overall (37% ALL, 40% AML) post-baseline, and the incidence of grade 3 or 4 ALT shifted from 2% overall (2% ALL,

2% AML) at baseline to 44% overall (43% ALL, 44% AML) post-baseline. Two patients showed improvement in ALT (1 ALL patient and 1 AML patient) or AST (1 AML patient) from grade 1 at baseline to within the normal range post-baseline. In addition, 3 patients (2 ALL, 1 AML) showed improvement in AST from grade 2 at baseline to grade 1 post-baseline.

ILEX's clinical interpretation for patients who have follow-up data determined that elevations in AST and ALT were transient and typically of <2 weeks duration. The majority of AST and ALT elevations occurred within 1 week of clofarabine administration and returned to baseline or ≤ grade 2 within several days. ILEX believes these elevations in AST and ALT were not clinically significant because they did not typically impact the delivery of the next cycle of therapy or hinder continuing to transplant. Although less common and of lower toxicity grade, elevations in bilirubin appeared to be more persistent.

A total of 46% of patients overall (46% ALL, 47% AML) experienced the onset or worsening of elevated total bilirubin during treatment with clofarabine. No patient had a grade 3 or 4 total bilirubin at baseline, while 15% overall (15% ALL, 16% AML) had a grade 3 or 4 total bilirubin post-baseline. The remainder of the post-baseline shifts to elevated levels (34 of 51) were to grade 1 or grade 2. One patient (ALL) had an improvement in total bilirubin from grade 2 at baseline to normal post-baseline. Two patients discontinued treatment with clofarabine due to the onset of grade 4 hyperbilirubinemia. Where follow-up data are available, bilirubin elevations took from 4 days to 32 days to return to baseline or ≤ grade 2.

A total of 23% of patients overall (28% ALL, 15% AML) experienced the onset or worsening of elevated alkaline phosphatase. No patient had grade 3 or 4 alkaline phosphatase at baseline, and only 1 patient (ALL) had post-baseline grade 3 or 4 alkaline phosphatase (specifically, grade 3). The remainder of the post-baseline shifts to elevated levels (22 of 23) were to grade 1 or 2. For 2 patients (both AML), alkaline phosphatase improved from grade 1 at baseline to within the normal range post-baseline.

6.3.5.3. Renal System

The most prevalent renal toxicity observed in pediatric patients exposed to clofarabine was elevated creatinine. However, despite clofarabine clearance through the kidneys, the direct effect on the kidney is thought to be minimal based on the preclinical toxicity data. The occurrence of renal impairment was likely influenced by the use of concurrent medications with known nephrotoxicity, such as amphotericin B, tobramycin, and vancomycin. In addition, tumor lysis with concurrent hyperuricemia may have also contributed to the development of renal insufficiency, as well as hypovolemia and hypotension.

A total of 43% of patients overall (43% ALL, 44% AML) experienced the onset or worsening of elevated creatinine. The incidence of grade 3 or 4 elevated creatinine shifted from 0% overall at baseline to 5% overall (6% ALL, 4% AML) post-baseline. The remainder of the post-baseline shifts to elevated levels of creatinine (43 of 49 shifts) were to grade 1 or 2. This could be as a result of tumor lysis syndrome or the effects of such concomitant medications as amphotericin B, aminoglycoside, or vancomycin. Patients had elevated creatinine levels that lasted from 1 to 22 days. For some patients the creatinine elevation was present at end of study or death. The duration of creatinine elevation correlated with concurrent conditions that most likely contributed to the renal toxicity.

6.3.5.4. Capillary Leak Syndrome and Systemic Inflammatory Response Syndrome

A SIRS/capillary leak-like syndrome, manifested by the rapid onset of respiratory distress, hypotension, and multi-organ failure, has been associated with many oncolytics including cytarabine, gemcitabine, rituximab, taxotere, and possibly cladribine.[70,71,72,73,74] The precise pathophysiology of SIRS/capillary leak syndrome is not entirely understood. It may result from the release of cytokines and may also reflect either direct or indirect damage to endothelial cells. In addition, it is believed that patients with rapid tumor lysis may be at particular risk for SIRS/capillary leak syndrome.[74,75] The clofarabine pediatric safety database was reviewed for these syndromes because ILEX noted the potential occurrence of signs or symptoms of these syndromes occurring in several patients.

Capillary leak syndrome or SIRS occurred in 4 pediatric patients overall (3 ALL, 1 AML).

CAPILLARY LEAK SYNDROME

Two patients died with grade 4 capillary leak syndrome, and 1 patient experienced hepatic toxicity in addition to grade 3 capillary leak syndrome at the 52 mg/m^2/day dose. In the 2 patients who died with capillary leak syndrome, the syndrome began on Day 23 and Day 17. The third patient received 4 doses of clofarabine 52 mg/m^2/day. His fifth dose was not administered due to the onset of the hepatic toxicity and capillary leak syndrome. Each event of capillary leak syndrome was reported as an SAE, and the investigators considered each event related to study drug.

Other concurrent medical conditions, including sepsis, may have contributed to the incidence of capillary leak syndrome. In addition, prior or concomitant therapies (eg, granulocyte colony stimulating factor [G-CSF]) and/or disease progression may also have made these patients more susceptible to capillary leak syndrome.

SIRS

Only 1 case of SIRS (in a patient with AML) was reported by the investigator. This patient received 4 doses of clofarabine 52 mg/m^2/day. His fifth dose was not administered due to the onset of grade 3 hypotension, fever neutropenia, SIRS, and serum sickness.

SIRS has been associated with most nucleoside analogues, including cytarabine, gemcitabine, and likely cladribine. It has also been reported in association with taxotere, IL-2, and granulocyte-macrophage colony stimulating factor (GM-CSF).[72,73,75,76] SIRS/capillary leak-like syndrome may also be associated with rapid tumor cell lysis and release of intracellular contents, including cytokines, which are likely to mediate these syndromes.[77] In this regard, SIRS/capillary leak syndrome could be an indirect result of the anti-tumor activity of clofarabine.

In this heavily treated, immunocompromised population it is difficult to fully understand the potential association between clofarabine and these syndromes. Many other factors could play a role in the development of this constellation of symptoms, including underlying infection, concomitant medications, progressive disease, and organ damage associated with prior high-dose chemotherapy and total body irradiation for transplant.

Typically SIRS is manifested by the rapid development of tachypnoea, tachycardia, hypotension, shock, and multi-organ failure. "Cytokine storm" has also been observed with other agents, including rituximab.[74] The relationship between "cytokine storm" and SIRS/capillary leak syndrome is not clear; however, it is possible that release of cytokines contributes to development of SIRS/capillary leak syndrome.

6.3.5.5. Cardiovascular System

Early preclinical studies indicated some potential cardiotoxicity, so ILEX incorporated additional cardiovascular preclinical studies into the developmental plan. These preclinical studies are summarized below.

There were no cardiac findings in the dog or mouse at lethal doses in the acute toxicology studies. There was, however, cardiac toxicity seen in rats dosed daily × 5 at the 300 mg/m^2 dose level when administered as a 1 to 2 minute bolus. The Cmax for clofarabine at this dose level was estimated at 120 µg/mL. Histological changes observed included myofiber degeneration, myocardial edema, neutrophilic infiltration, and endomysial proliferation. Lesions were restricted to the left atrium and ventricle and interventricular septum. No cardiac lesions were observed at 150 mg/m^2/day (clofarabine Cmax estimated at 20 µg/mL). When the clofarabine infusion was prolonged to 60 minutes there was a remarkable reduction in the cardiac findings in the rat at 300 mg/m^2/day with no myocardial degeneration. However, endomysial proliferation was seen in surviving rats at 30 days.

Additional preclinical studies were performed on rats to further investigate this cardiotoxicity. These included a study of cardiac biomarkers that was performed in rats dosed daily × 5 at 75, 150, and 300 mg/m^2/day. No abnormalities in troponin I or CK-MB were observed at 75 or 150 mg/m^2/day on Days 1, 5, and 8 after dosing. At the 300 mg/m^2/day dose level there were no changes in troponin I, but there were increases on CK-MB in moribund rats. An additional study showed that clofarabine interfered with adenosine receptor (A_1, A_{2A}, and A_3) binding at a concentration of approximately 3 µg/mL. It should be noted that cladribine, a drug related to clofarabine, has also been shown to

activate the adenosine receptor.[78] It is also worth noting that high doses of adenosine have been reported to cause hypotension.[79]

In response to these findings of significant cardiotoxicity in rats, and after discussion with the FDA, cardiac monitoring was included in the 2 pivotal studies in children with ALL (CLO-212) and AML (CLO-222).

Initially, ECHOs or multiple gated acquisition (MUGA) cardiac angiograms were requested prior to entrance onto the study, and again, after completion of 4 cycles of therapy. In addition, frequent monitoring of vital signs was required. Since there was an indication that the severity of cardiotoxicity was related to the Cmax of clofarabine, in the rat, the infusion time for clofarabine was specified to be 2 hours in all patients in the clinical studies. It was anticipated that monitoring along with frequent assessment of vital signs, would capture data related to cardiac function, as well as changes in blood pressure that could be indicative of adenosine receptor activation.

Data from the ECHOs and MUGAs were incorporated, as interpreted and reported by the individual participating institutions, into a database (the integrated safety database) including CLO-212 (ALL) patients, CLO-222 (AML) patients, the pediatric patient in study CLO-141 and the 1 pediatric patient in study CLO-221.

Tabulation of the data compiled in this manner yielded the results in the subsections that follow.

MUGA SCANS

Only 7 of the 113 patients (6%) in the integrated safety database had a MUGA scan at baseline. These included 2 ALL patients (from CLO-212) and 5 AML patients (from CLO-141 [n=1], CLO-221 [n=1], and CLO-222 [n=3]). Only 2 of these patients had a MUGA scan performed at the end of the study (2 AML patients). All these MUGAs were normal.

ECHOCARDIOGRAMS

A total of 47 of 113 (42%) patients in the integrated database had both a baseline and a subsequent ECHO. This included 42% [28/67] of patients with ALL and 41% [19/46] of patients with AML. Most patients (26/47, 55%) had no adverse changes on the follow up ECHOs. A total of 21% of patients [11/47], including 5 patients with ALL and 6 patients with AML, developed abnormalities on the follow up ECHOs that were not present at baseline. One of the patients with ALL had a normal MUGA scan at study entry instead of an ECHO, but had an abnormal ECHO at the end of study. The remaining patients had ECHOs that were abnormal at baseline and remained abnormal.

The characteristics of the 5 ALL patients with deterioration of their ECHOs from normal to abnormal were:

- Patient 1) Normal ECHO at study entry. Ejection fraction was decreased from a baseline of 69% to 56%, 3 days after completing Day 4 of Cycle 1 (end of study evaluation). At this time, the patient was hypotensive and septic with blood cultures positive for *Enterobacter*, *S. viridans*, and *Candida*. There was subsequent recovery of left ventricular (LV) function.

- Patient 2) Normal ECHO at study entry. Developed elevated right ventricular systolic pressure (40 mm Hg) and a pericardial effusion (PE) noted at the end of study evaluation (13 days after the fourth dose of Cycle 2). This follow-up ECHO was obtained during a period of progressive *Aspergillus* infection.

- Patient 3) Normal ECHO at study entry. The follow-up ECHO revealed low normal to mildly abnormal LV systolic function with a left ventricular internal dimension (LVID) in the upper limit of normal range for the patient's BSA. There was also a small PE noted 12 days after completing Cycle 1 and again at the end of study evaluation (Day 2 of Cycle 2).

- Patient 4) Normal ECHO at study entry. Mitral regurgitation, tricuspid regurgitation, pulmonary regurgitation, and aortic regurgitation, with mild to moderate depressed left ventricular systolic function (left ventricular shortening fraction of 22%) noted at the end of study evaluation (17 days after completing Cycle 1). This follow-up ECHO was obtained when the patient was experiencing electrolyte abnormalities and was septic with *Candida tropicalis*.

- Patient 5) MUGA was performed at study entry and therefore this patient did not have a baseline ECHO. A small PE, abnormal fractional shortening (24%) and increased left ventricular pre-ejection period/ejection time ratio were noted on the ECHO performed at the end of study evaluation (9 days after completing Cycle 2).

The characteristics of the 6 AML patients with ECHO deterioration from baseline normal to end-of-study abnormal were:

- Patient 1) Normal ECHO at study entry. There was a marked reduction in left ventricular systolic function (20% shortening fraction), and a very small PE 6 days documented after completing Cycle 1 (end of study). This patient was discontinued due to grade 4 ventricular arrhythmia NOS that appeared to be related to an antifungal drug.

- Patient 2) Normal ECHO at study entry. Borderline right ventricular enlargement noted on Day 5 of Cycle 3 (end of study). The patient did not receive Day 5 of Cycle 3 due to septic shock secondary to patient's disease that resulted in death the next day.

- Patient 3) Normal ECHO at study entry. Mildly reduced left ventricular systolic function with an ejection fraction of 45% to 50% documented 23 days after completing Cycle 2 (end of study).

- Patient 4) Normal ECHO at study entry. Low velocity tricuspid regurgitation noted 7 days after completing Cycle 2 (end of study).

- Patient 5) Normal ECHO at study entry. Borderline left ventricular systolic function documented 3 days after completing Cycle 1 (end of study). This represented a small decrease in shortening fraction compared to the ECHO at study entry.

- Patient 6) Normal ECHO at study entry. Mildly to moderately diminished systolic function (shortening fraction 28%), a small PE, moderate concentric left ventricular hypertrophy, and no significant pleural effusion noted in the setting of pressors on Day 4 of Cycle 2 (end of study). The patient died the same day from drug-related septic shock and drug-related multi-organ failure.

To further analyze the cardiac data, ILEX requested that L Steinherz MD, a board-certified pediatric cardiologist, conduct an independent review of the ECHO and MUGA reports submitted on the patients in the "pivotal" Phase II trials (CLO-212 and CLO-222.
Dr Steinherz identified a total of 24 patients (12/32 patients with ALL and 12/23 patients

with AML) whose cardiac studies became abnormal (PE and LVSD) while on study. A brief summary of her findings is presented in the indented text below:

> Pericardial effusion was a frequent finding in these patients on post treatment studies, (9/32, 28% of patients with ALL in CLO-212 and 10/23, 43% of patients with AML in CLO-222). Of note, 2 of these patients with ALL and 2 patients with AML already had peridcardial effusion at baseline. The effusion was almost always minimal to small and never had any hemodynamic significance.
>
> LVSD was also noted. Six of 32 (19%) patients with ALL in CLO-212 and 9/23 (39%) patients with AML in CLO-222 had some evidence of LVSD after study entry. In most cases where subsequent follow-up data were available, the LVSD appeared to be transient. The exact etiology for the LVSD is not clear. While direct cardiotoxicity of clofarabine cannot be completely ruled out, the patients in this study who had mild-to-moderate LVSD also had other factors that were possibly responsible for the LVSD. In nearly all of the cases of LVSD, patients were being treated for serious concurrent illnesses, such as culture-positive bacterial or fungal sepsis, around the time of the follow-up ECHOs. Several had an episode of severe hypotension close to the time of the follow up cardiac study. A few patients came on study with a history of serious pre-existing illness, known to potentially involve cardiac abnormalities, (eg, sickle cell disease). These are all factors that could have negatively impacted cardiac function. In addition, all patients had already received significant amounts of anthracyclines before study entry. In several patients, the clofarabine treatment was initiated close enough to the last anthracycline dose (within 4 months) for the LVSD to have possibly been reflecting deterioration due to the anthracycline. Other patients had received high-dose cyclophosphamide and TBI as part of a conditioning regimen for BMT close to the time of clofarabine therapy. It is possible that the PE and, in some patients, the LVSD could be the effect of fluid retention from cytokine release resulting from tumor lysis. Unfortunately in some patients the off-study ECHOs were performed at times when the patients were severely ill and even pre-terminal from disease progression.
>
> It should be noted that in at least 1 patient with severely reduced cardiac function at baseline (shortening fraction of 20%), clofarabine was tolerated with no significant further reduction in cardiac function.

To get a clearer assessment of cardiac function, ILEX expanded cardiac monitoring. To date, 10 patients (4 with ALL, 6 with AML; 2 each that had data included in the updated ISS) have been enrolled and treated under the increased cardiac monitoring specifications.

In addition to the interpretation of ECHOs and the pediatric cardiologist's review of patient data, ILEX obtained autopsy results on 4 patients who were included in the July submission of the Integrated Summary of Safety (ISS) and the Integrated Summary of Efficacy (ISE). Two of these patients (both with ALL) had received 1 cycle of clofarabine each and had no cardiac abnormalities noted by histopathology. One patient had received 1 cycle of clofarabine and had cardiac abnormalities noted, and an additional patient had received 2 cycles of clofarabine and had cardiac abnormalities noted at autopsy. Histopathology for both these patients is now being reviewed in comparison to the findings noted in the rat. It should be noted that, in general, these patients had been exposed to a variety of high-dose chemotherapy regimens, including anthracyclines, high-dose cytoxan, and TBI, all potentially cardiotoxic treatments or regimens.

HYPOTENSION

In the integrated database, 27% of patients overall (25% ALL, 30% AML) experienced hypotension, and 18% overall (16% ALL, 20% AML) had a grade 3 or grade 4 event of hypotension. The following special analysis of hypotension was conducted for the pivotal ILEX trials, CLO-212 and CLO-222.

A total of 22/84 patients (26%, 12 ALL, 10 AML) had an AE of hypotension. Seventeen of these 22 patients (77%, 9 ALL, 8 AML) also had a concomitant high-grade infection at the time of the hypotension. The concomitant infections associated with the hypotension were nonspecific sepsis, septic shock, pneumonia, fungal pneumonia, *herpes esophagitis*, *Staphylococcus* and *Escherichia coli* sepsis, and gram-negative sepsis. Five patients (5/22-23%, 3 ALL, 2 AML) did not have clear evidence of severe infection associated with their hypotension. The duration of the hypotensive episodes was typically from 1 to 15 days and was closely associated with the duration of the concurrent event, ie, infection.

In conclusion, 12 patients with ALL and 10 patients with AML developed treatment-emergent hypotension. The treatment-emergent hypotensive episodes appear to be related to severe or systemic infections. Patients who had hypotension that was associated with an infection tended not to experience hypotension during subsequent cycles of treatment, and

patients with infections who were able to recover bone marrow function tended not to become septic or hypotensive. It should also be noted that since clofarabine at high doses could activate the adenosine receptor, hypotension could result especially in patients with limited capacity to compensate. This could be most relevant for patients on cardiac medications (e.g. antihypertensives) or those with already impaired cardiac function.

6.3.6. Other Laboratory Tests

Data for vital signs and physical examinations were collected in studies CLO-212, CLO-221, CLO–222, and ID99-383. Abnormalities noted during these examinations were to be reported as AEs. Therefore, the vital signs data were not analyzed further.

6.3.7. Safety Summary

It is worth noting that a large number of the adverse effects were already present in many of the patients at baseline. In fact, 98% of the patients in the 2 pivotal Phase II studies had at least 1 concurrent condition at baseline. The most frequent pre-existing conditions included alopecia, tachycardia, fatigue, pyrexia, nausea, anorexia, and vomiting, each of which was present in at least 20% of the patients at baseline. The most common on-study toxicities, regardless of causality, that were observed during exposure to clofarabine were gastrointestinal system AEs, including vomiting, nausea, and diarrhea; adverse hematologic effects, including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile neutropenia; and infection.

ILEX continued to refine patient selection and management for the clofarabine pediatric studies. In this regard, some of the steps ILEX took include encouraging the investigators to use extra fluids during Cycle 1 to reduce the effects of tumor lysis and its manifestations, and modifying the entry criteria to enroll patients with fewer pre-existing severe infections and to eliminate patients who have undergone a HSCT within 3 months prior to clofarabine treatment. The goal of these modifications was to continue improving the tolerability of clofarabine and to enroll patients with less compromised organ function. Under this approach we treated a total of 13 patients (8 ALL, 5 AML) with a total of 6 patients reporting

SAEs and 0 deaths on study. Due to better screening and supportive care of clofarabine-treated patients, the safety profile of clofarabine has improved.

An analysis of the CLO-212 patients treated under better selection criteria and supportive care (described above) revealed that only 4 of the 8 patients reported SAEs and there were no deaths on study as of data cut-off.

- Patient 1 had an SAE of diarrhea unrelated to study drug and an SAE of febrile neutropenia related to study drug;
- Patient 2 had an SAE of febrile neutropenia possibly related to study drug;
- Patient 3 had an SAE of jaw/neck pain (aphthous ulcer) unrelated to study drug; and
- Patient 4 had SAEs of sepsis (*Streptococcus viridans*) related to study drug and fungal infection unrelated to study drug. This patient began treatment with clofarabine on 05 May 2004 and had an SAE of acute renal failure unrelated to study drug (uric acid was 17.8 mg/dL on 10 May 2004). This indicates that the acute renal failure was most likely due to tumor lysis. The hyperuricemia resolved the next day (uric acid <0.2 mg/dL on 11 May 2004). The patient also had an SAE of cholestasis related to study drug.

An analysis of the CLO-222 patients treated under better selection criteria and supportive care (described above) revealed that only 2 of the 5 patients reported SAEs and there were no deaths on study as of data cutoff.

- Patient 1 had an SAE of line infection unrelated to study drug; and
- Patient 2 had an SAE of febrile neutropenia related to study drug.

In conclusion, the safety profile for clofarabine remains as expected in this heavily pre-treated and generally immunocompromised patient population. The observed toxicities are acceptable considering the prognosis of these patients and the lack of other available treatments.

7. ADDITIONAL SAFETY INFORMATION

Limited data are available from the prior studies in adults and from ILEX's ongoing studies in adults for a variety of indications. These data are summarized below.

OTHER ONCOLOGY STUDIES: BRIEF SUMMARY OF CLOFARABINE IN ADULT SUBJECTS

ILEX has taken a broad approach to evaluating the activity and safety of clofarabine in patients with acute leukemia. While some studies have focused largely on the pediatric acute leukemias, other studies have been undertaken in adults. The major focus has been on adult AML as early studies suggested clofarabine may have activity in this disease entity. Since the single agent Phase I studies have been conducted, several Phase I and II studies have been undertaken in adults with AML. A discussion regarding a separate registration strategy for adults with acute leukemias is ongoing between ILEX and FDA.

A Phase I study (DM93-036) defined clofarabine 40 mg/m^2 daily for 5 days as the recommended Phase II dose in adult patients with acute leukemia. For adult patients with acute leukemia, the DLT was hepatotoxicity.[80]

In a follow-up Phase I ILEX study, CLO-141, clofarabine was escalated in doses of 15, 22.5, 30, and 40 mg/m^2 daily for 5 days (D2-6) in combination with ara-C 1 g/m^2 daily for 5 days (D1-5) in adults with acute leukemia. No DLTs were observed and clofarabine 40 mg/m^2/day was chosen as the Phase II dose in combination with ara-C.[81] Currently, clofarabine is being investigated in adult patients with acute leukemia using various doses of clofarabine alone and in combination with other drugs.

A summary of the adult studies is provided in Table 46, and includes publications for each study and a brief description of the efficacy, safety, and conclusions.

Table 46: Summary of Clinical Studies in Adult AML

Study ID	Publications	Efficacy	Safety	Conclusions
CLO-221 ILEX	Foran JM, Faderl S, Wetzler M, et al. Proc Am Soc Clin Oncol 2003;22:587. Abs 2360 Foran J, Wetzler M, Kantarjian H, et al. Blood 2002; 100(11):271b. Abs 4613.	22 patients 1 IRRP CR (duration of remission 20.4 weeks) 1 investigator PR 1 TF proceeded to transplant Median survival 3.2 months (0.6 to 10.1 months)	Most common drug-related AEs: nausea, vomiting, headache, diarrhea, anorexia, dermatitis, and stomatitis Grade 3 or 4 AE reported by ≥20% patients was febrile neutropenia Drug-related renal toxicities reported for 10% patients	Limited efficacy activity in this population of multiply relapsed or refractory patients; safety profile as expected in this population
CLO-141 ILEX	Faderl S, Gandhi V, Cortes J, et al. Proc Am Soc Clin Oncol 2003;22:586. Abs 2355 Faderl S, Gandhi V, Garcia-Manero G, et al. Blood 2003; 102(11):615a. Abs 2271	32 patients, efficacy for 29 7/29 (24%) CR 5/29 (17%) CRp OR=41% (12/29) MTD was 40 mg/m^2/day	Most common drug-related AEs: nausea, diarrhea, vomiting, dermatitis, flushing, palmar-plantar erythrodysesthesia syndrome, and headache Changes in chemistry parameters mild to moderate and reversible if not attributable to disease. Bone marrow function was suppressed, resulting in neutropenia, lymphocytopenia, anemia, and thrombocytopenia.	Preliminary results suggest that clofarabine could be combined with Ara-C at full doses for a favorable response. The combination is very active in this population and suggests use in patients >60 years of age may be of particular interest.

Table 46: Summary of Clinical Studies in Adult AML (continued)

Study ID	Publications	Efficacy	Safety	Conclusions
iCLO002 Dr Faderl	Faderl S, Gandhi V, Giles F, et al. Proc Am Soc Clin Oncol 2004;22(14s):584s. Abs 6609	60 patients 31/60 (52%) CR 5/60 (8%) CRp Median time to CR was 29 days (20 to 98)	9 deaths on study AEs: transient facial flushing and headaches (grade <3) during infusion and hyperbilirubinemia (grade 3 in 3 patients), skin rashes, increased AST/ALT, palmar-plantar erythrodysesthesia, pancreatitis (1 patient), and renal failure (1 patient)	Preliminary results continue to support the combination of clofarabine and Ara-C as active in older patients with AML. Safety profile appears to be acceptable.
IST Dr Burnett	--	Data for 16 patients 10/16 (63%) CR with 1 cycle, 4 no response, 2 died	Grade ≤2 liver toxicity in 12/16 patients (75%), Grade 3 in 3/16 patients (19%), and no Grade 4. Some hematologic toxicity noted.	Preliminary data suggest activity of single-agent clofarabine in remission induction of newly diagnosed, previously untreated older patients with AML. Response rate to single-agent clofarabine appears at least comparable to many combination studies.
iCLO011 Dr Faderl	--	7 patients enrolled (3 clofarabine + ara-C and 4 single-agent clofarabine) Too early to assess efficacy	Too early to assess safety	Too early for conclusions
iCLO0004 Dr Foran	--	4 patients treated Too early to assess efficacy	Too early to assess safety	Too early for conclusions

8. BENEFIT/RISK DISCUSSION

8.1. Overview

There are limited therapeutic options for this multiply relapsed, highly refractory pediatric population. The prognosis for these patients is dismal with no realistic chance for survival even with currently available therapies, with the possible exception of transplant. Although progress has been made in the management of various types of leukemia, patients who have had multiple relapses usually die from progressive disease.[82] As this population has few effective options for treatment, they are frequently placed on palliative care with agents such as oral etoposide. Since significant numbers of children still die of this disease, new treatment options such as clofarabine are needed.[83]

The population of multiply relapsed and/or refractory pediatric patients with acute leukemia has had limited opportunities to participate in many Phase II clinical trials. Although numerous agents are investigated in small Phase I trials, other pediatric Phase II studies—whether single-agent or multi-agent trials—study less heavily pretreated patients than were included in ILEX's pivotal Phase II studies. For example, in 1 of the few studies of refractory pediatric AML—a study involving the use of Homoharringtonine—the entry criteria excluded patients who had undergone more than 2 prior treatment regimens and patients who had participated in >1 Phase II trial.[84] More than half the patients in ILEX's CLO-222 pivotal trial would not have been eligible for this study because of the limitation on the number of prior treatment regimens.

In conclusion, pediatric patients with refractory or relapsed ALL and AML clearly constitute a population with an unmet medical need.

8.2. Benefits of Clofarabine Treatment

The pediatric leukemia patients in ID99-383, CLO-212, and CLO-222 have shown prospectively defined, independently confirmed CR, CRp, and PR, many of which had durable remission or other clinical benefit such as proceeding to transplant. Clofarabine-treated patients with acceptable donors have proceeded to transplant with prolonged survival.

Even some clofarabine-treated patients who did not meet the response criteria have sustained sufficient clinical benefit to proceed to transplant. Overall the safety profile does not appear substantially different from what has been previously reported, even when compared to some studies that were conducted in less heavily pretreated patients with ALL or AML.

For the 2 pivotal Phase II studies, a combined total of 6 patients (6/84) achieved a CR, 5 patients (5/84) achieved a CRp, and 13 patients (13/84) achieved a PR. A total of 19 patients from the 2 pivotal Phase II studies received clinical benefit from clofarabine and proceeded to transplant. An additional 3 patients (from CLO-212) who did not proceed to transplant nonetheless had a durable remission (ie, ≥8 weeks): 2 patients with a response of CR and 1 with a response of CRp (all from CLO-212).

In the Phase I dose-escalation study, ID99-383, 7/25 patients received clinical benefit and proceeded to transplant after treatment with single-agent clofarabine. Of these 7 patients, only 4 were IRRP-confirmed responders. Two of the 3 additional patients from ID99-383 had AML with an investigator determination of response as PR and "improvement," and 1 patient had ALL and an investigator determination of response as "improvement." Thus a combined total of 29 patients from these 3 studies, CLO-212, CLO-222, and ID99-383, have received clinical benefit from single-agent treatment with clofarabine by proceeding to transplant or sustaining durable remission.

Furthermore, a combined total of 42/70 patients from CLO-212 and CLO-222 who had on-study KPS scores (60%) had scores that stayed the same (27 patients, 38.6%) or improved (15 patients, 21.4%). Considering the condition of these patients and the fact that they were undergoing yet another chemotherapy regimen, it is noteworthy that half of these patients had KPS values that either stayed the same or improved. These data were slightly more impressive for the patients with AML in CLO-222 (71.4%), than for the patients with ALL in CLO-212 (52.4%).

8.3. Risks Associated with Clofarabine Treatment

The most commonly reported events of grade 3 or 4 severity were febrile neutropenia (grade 3, 54%; grade 4, 4%), nausea (grade 3, 15%; grade 4, 1%), pyrexia (grade 3, 15%; grade 4, 0%), and epistaxis (grade 3, 14%; grade 4, 0%). Most of these events can also be a result of the patient's underlying disease and are typical of most chemotherapy agents.

Additional toxicities noted include the following:

- Transient elevations in AST and ALT, typically of <2 weeks duration were observed and generally not considered to be clinically significant. Although less common, there were also elevations in bilirubin, which took from 4 to 32 days to return to baseline or ≤ grade 2. The increases in transaminases and bilirubin could also have been influenced by the use of concomitant medications, eg, voriconazole and cyclosporine.

- Increases in creatinine were observed in some patients. However, the majority of these increases occurred in patients with other concurrent disease processes (eg, sepsis, tumor lysis) or concomitant medications, (eg, amphotericin B, aminoglycoside use, or vancomycin). Duration of elevated creatinine ranged from 1 to 22 days, and appeared to be associated with the duration of the underlying condition.

- SIRS and capillary leak syndrome were observed in several patients. This disorder has been associated with many oncolytics, including cytarabine, gemcitabine, taxotere, and possibly cladribine. It should also be noted that underlying toxicities from prior therapies, infections, or disease progression may not only cause many of the same symptoms of SIRS/capillary leak syndrome, but may also predispose patients to this condition.

- Based on preclinical data in 1 species and in agreement with the FDA, cardiac function was monitored in these studies. Decline in cardiac function was observed in several patients; however, follow-up ECHOs were frequently performed at times when the patients were ill from disease progression, sepsis, or following the development of other substantial medical conditions. Twelve patients with ALL and 10 patients with AML developed treatment-emergent hypotension. These episodes appear to be related to severe or systemic infections in the vast majority of cases. Patients who had hypotension associated with an infection tended not to experience hypotension during subsequent cycles of treatment.

8.4. Overall Conclusions of Benefit–Risk Assessment

These Phase II pivotal studies have shown the efficacy of clofarabine in obtaining remissions in this multiply relapsed, resistant population, or substantial cytoreduction that allowed patients to proceed to transplant. In this highly refractory population with an unmet medical need, the response rate is impressive, particularly considering the extent of prior treatments and the number of concurrent illnesses and concomitant medications. The safety profile for clofarabine is acceptable and predictable in this heavily pretreated population of patients who have limited options. In addition, ILEX anticipates that the safety profile of clofarabine will improve in less heavily pretreated patients.

ILEX contends that close monitoring and early intervention may mitigate the severity of the toxicities associated with clofarabine. In this regard, ILEX has advised investigators to be alert to early indications of clofarabine-related toxicities (eg, capillary leak) and to immediately discontinue clofarabine administration and provide appropriate supportive care. After the patient is stabilized, clofarabine may be reinstituted, possibly at a lower dose. ILEX continues to monitor patients closely for toxicities in its ongoing safety efforts, with a goal of identifying patients at a particularly high risk.

Despite closure of the pivotal studies, there is continuing demand for access to clofarabine through the EEAP. Patients from Canada, South America, Europe, Puerto Rico, as well as patients in the US have sought access to clofarabine and many have been treated.

In conclusion, clofarabine represents an additional option to a patient population that has failed available therapies. Clofarabine has been shown to be effective in this population of patients who have developed highly cross-resistant disease. For those patients or families who seek an additional treatment option, clofarabine has provided clinical benefit to patients who achieved durable remission or lowered the tumor burden and proceeded to transplant. This treatment has provided these patients the possibility of increased survival. As there has been little published data regarding the survival of patients with ALL and AML in second, third, or subsequent relapse, it is difficult to compare the results from ILEX's studies to other therapies. However, long-term survival in these multiply relapsed and refractory patients is

poor. In this regard, clofarabine represents an important advance in the treatment of relapsed or refractory acute pediatric leukemias, with a favorable benefit-risk relationship in this population that justifies the commercial availability of this product.

9. RESPONDER NARRATIVES FROM THE PIVOTAL PHASE II STUDIES

9.1. Responder Narratives from CLO-212

The narratives provided in this appendix, include the original narratives submitted to the FDA in March, along with an updated section at the end of some narratives that contains new data received for the 120-day update.

Complete Responders

Patient 212-006-0047 was a 12-year-old Hispanic male diagnosed with ALL on 16 July 2003. He received 4 prior induction regimens, all with a best response of treatment failure, before entering this study.

- July 2003 to August 2003 – 1 induction regimen of prednisone, vincristine, doxorubicin, dexrazoxane, methotrexate HD, leucovorin, L-asparaginase, and IT cytarabine and methotrexate.
- August 2003 – 1 induction regimen of cytarabine and L-asparaginase.
- October 2003 – 1 induction regimen of dexamethasone and etoposide
- November 2003 – 1 induction regimen of etoposide, ifosfamide, carboplatin, and IT methotrexate and cytarabine.

The patient entered this study on 26 November 2003 with 67% bone marrow blasts and received 2 cycles of clofarabine. For cycle 1 he was dosed at 52 mg/m^2/day from 01 December 2003 to 05 December 2003. The principal investigator requested dose reduction for cycle 2 secondary to myelosuppression with complications of pneumonia, therefore the patient was dosed at 39 mg/m^2/day from 06 January 2004 to 10 January 2004. He achieved a CR according to the investigator on 10 January 2004 (Cycle 2) with 0% bone marrow blasts (22 December 2003), ANC 2.480×10^9/L, and platelets 104×10^9/L (10 January 2004). The CR was confirmed by the IRRP. He relapsed on 10 February 2004 with 44% blasts in the marrow. No further follow-up data are available. In summary, this patient achieved a CR 5.7 weeks after starting treatment with clofarabine, which endured 4.3 weeks. Overall survival was 10.4+ weeks as of last follow up on 12 February 2004.

Patient 212-009-0045 was an 11-year-old Caucasian female diagnosed with ALL on 01 June 1995. She received 2 prior induction regimens and 2 post induction regimens before entering this study.

- June 1995 to August 1997 – 1 induction regimen of prednisone, vincristine, and L-asparaginase with IT methotrexate and hydrocortisone, followed by post induction regimen of methotrexate, 6-mercaptoprine, and leucovorin, with IT methotrexate, hydrocortisone, and cytarabine (per POG 9405) with a best response of CR.

- November 1999 to April 2002 – 1 induction regimen of decadron (HD), vincristine, L-asparaginase, and adriamycin with IT methotrexate, hydrocortisone, and cytarabine, followed by vincristine, etoposide, cytarabine, adriamycin, cytoxan, decadron, methotrexate,

- 6-mercaptopurine (HD), leucovorin, and PEG-asparaginase with IT methotrexate, hydrocortisone, and cytarabine (per POG 9310, +9605) with a best response of CR.

This patient entered the study on 20 November 2003 with 86% bone marrow blasts and received 2 cycles of clofarabine 52 mg/m^2/day from 20 November 2003 to 23 December 2003. She achieved a CR according to the investigator on 15 December 2003 (Cycle 1) with 1% blasts and a normocellular marrow, which was confirmed by the IRRP (19 December 2003 per marrow and peripheral counts). She was discontinued from the study on 14 January 2004 to receive a transplant. She had 5% blasts with a normocellular marrow on 20 January 2004 and was treated with ifosfamide, VP-16, and MESNA on 22 January 2004 as preparation for transplant. Blasts were 0% with a hypocellular marrow on 10 February 2004. She underwent TBI and received a cord blood transplant from a matched, unrelated donor (4/6) on 24 February 2004. The patient was alive as of last follow up on 22 March 2004. In summary, this patient achieved a CR 4.1 weeks after starting treatment with clofarabine, which endured 13.4+ weeks. Post-transplant survival was 3.9+ weeks and overall survival was 17.6+ weeks.

Patient 212-014-0049 was a 12-year-old Hispanic female diagnosed with ALL on 07 October 1993. She received 3 prior induction regimens and 3 post induction regimens before entering this study.

- October 1993 to September 1995 – 1 induction regimen of L-asparaginase, vincristine, and prednisone with IT methotrexate, hydrocortisone, and cytarabine followed by post-induction vincristine, L-asparaginase, prednisone, 6-mercaptopurine, and methotrexate with IT methotrexate, hydrocortisone, and cytarabine with a best response of CR.

- September 1995 to August 1997 – 1 induction regimen of thiotepa, vincristine, dexamethasone, and PEG-asparaginase with IT methotrexate and cytarabine followed by post-induction 6-thioguanine, cyclophosphamide, vincristine, dexamethasone, methotrexate (HD), leucovorin, etoposide, cytarabine (HD), and 6-mercaptopurine with IT methotrexate and cytarabine for a best response of CR.

- April 1998 to February 1999 – 1 induction regimen of PEG-asparaginase, thiotepa, vincristine, and dexamethasone with IT methotrexate, cytarabine and hydrocortisone followed by post induction leucovorin, 6-thioguanine, cyclophosphamide, vincristine, dexamethasone, methotrexate (HD), etoposide, cytarabine (HD), and thiotepa with IT methotrexate and cytarabine for a best response of CR.

The patient entered this study on 16 December 2003 with 68% bone marrow blasts and received 5 cycles of clofarabine: 2 cycles of 52 mg/m^2/day from 17 December 2003 to 16 January 2004 and 3 cycles of 40 mg/m^2/day from 09 February 2004 to 09 April 2004. The dose was reduced due to febrile neutropenia (grade 3). She achieved CR according to the investigator on 09 January 2004 (Cycle 1) with 1% bone marrow blasts, which was confirmed by IRRP. Subsequent marrows were blasts 1% on 09 February 2004, blasts 2% on 05 March 2004 and blasts 1% on 05 April 2004. The patient continues on study. In summary, this patient achieved a CR 3.3 weeks after starting treatment with clofarabine, which endured 13+ weeks. Overall survival was 16.3+ weeks as of last follow up on 09 April 2004.

Patient 212-007-0018 was an 18-year-old Black female diagnosed with pre-B cell ALL on 27 October 2000. She received 3 prior induction chemotherapy regimens and 1 post-induction regimen before entering the study.

- October 2000 to June 2002 - 1 induction regimen of prednisone, vincristine, daunomycin, L-asparaginase, IT methotrexate, and IT cytarabine, followed by post-induction therapy with cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine, methotrexate, dexamethasone, doxorubicin, methotrexate PO, and 6-mercaptopurine. Treatment was according to protocol CCG 1961.

- August 2002 - 1 induction regimen of etoposide, ifosfamide, vincristine, dexamethasone, and MESNA according to protocol CCG 1951 and prophylactic IT methotrexate, IT cytarabine, and IT hydrocortisone, with a best response of treatment failure.

- October 2002 - 1 induction regimen of cytarabine and idarubicin, with a best response of treatment failure.

She entered the study on 25 October 2002 and received 3 cycles of clofarabine 52 mg/m^2/day from 28 October 2002 to 24 December 2002. She achieved a CR according to the investigator on 05 February 2003 (Cycle 3) with 0% bone marrow blasts and a normocellular marrow, which was confirmed by the IRRP. She was discontinued from the study on 26 February 2003 due to drug-related grade 4 hyperbilirubinemia, which was ongoing when she received alternative treatment. She was diagnosed with disease progression on 20 March 2003 and received 6-mercaptopurine and methotrexate with a response of treatment failure. She was still alive at the last follow-up on 15 September 2003. In summary, this patient achieved a CR 14.3 weeks after starting treatment with clofarabine, which endured for 6.1 weeks, and had an overall survival of 46.0+ weeks. Follow up information indicates that this patient died 12 December 2003, and overall survival was 58.6 weeks.

Patient 212-009-0028 was a 17-year-old Black male diagnosed with atypical B-cell ALL on 17 March 1999. He received 2 prior induction chemotherapy regimens, 2 post-induction regimens, and 1 prior transplant before entering the study:

- March 1999 to April 2001 - 1 cycle of daunomycin, prednisone, L-asparaginase, vincristine, and IT methotrexate, IT cytarabine, and IT hydrocortisone followed by post-induction therapy with 6-mercaptopurine, teniposide, cytarabine, daunomycin, vincristine, L-asparaginase, prednisone, etoposide, and IM methotrexate, IT hydrocortisone, IT cytarabine, and IT methotrexate with a best response of CR from April 1999 to April 2001.

- April 2001 to September 2001 - 1 cycle of daunomycin, prednisone, L-asparaginase, vincristine, and IT methotrexate followed by post-induction therapy with vincristine, etoposide, cytarabine, L-asparaginase, cyclophosphamide, prednisone, 6-mercaptopurine, and MESNA, and IT cytarabine and IT methotrexate with a best response of CR from 03 May 2001 to 13 September 2002.

- 28 September 2001 - a BMT from an unrelated donor (5/6 antigen match) conditioned with cyclophosphamide and TBI, with successful engraftment on 12 October 2001.

He entered the study on 22 May 2003 with 72% bone marrow blasts and received 3 cycles of clofarabine 52 mg/m^2/day from 22 May 2003 to 01 August 2003. According to the investigator, he achieved a PR on 10 June 2003 (after Cycle 1), which improved to a CRp (platelets = 36.0×10^9/L) on 22 July 2003 (after Cycle 2), with 0% blasts and a normocellular marrow. The IRRP considered the patient to have achieved a CR on 19 June 2003 (after 1 cycle). He was diagnosed with disease progression on 26 August 2003 and was discontinued from the study on 29 August 2003, at which time he received a therapeutic donor lymphocyte infusion. He was still alive at the last follow-up on 25 September 2003. In summary, this patient achieved a CR 4.0 weeks after starting treatment with clofarabine, which endured for 9.7 weeks, and had an overall survival of 18.0+ weeks. This patient was alive as of last follow up on 25 March 2004. Remission has endured for 9.7 weeks, and overall survival was 44.0+ weeks.

Patient 212-014-0030 was a 16-year-old Caucasian male diagnosed with pre-B cell ALL on 16 October 1991. He received 4 prior induction chemotherapy regimens, 3 post-induction regimens, and 2 prior transplants before entering the study.

- October 1991 to April 1994 - 1 cycle of prednisone, vincristine, L-asparaginase, IT cytarabine, IT methotrexate, and IT hydrocortisone, followed by post-induction therapy with methotrexate, cytarabine, prednisone, vincristine, 6-mercaptopurine, and PO methotrexate, and IT cytarabine, IT methotrexate, and IT hydrocortisone with a best response of CR from November 1991 to December 1998.

- December 1998 to July 1999 - 1 cycle of daunorubicin, vincristine, cyclophosphamide, asparaginase, and prednisone, and IT cytarabine, and IT methotrexate followed by post-induction therapy with asparaginase, cytarabine, methotrexate, vincristine, prednisone, asparaginase (Erwinia), 6-thioguanine, cyclophosphamide, daunorubicin, and IT methotrexate, with a best response of CR from January 1999 to November 2001.

- August 1999 - an allogenic cord blood transplant followed by an allogenic BMT conditioned with cyclophosphamide and TBI, with successful engraftment on 28 August 1999.

- November 2001 to July 2002 - 1 cycle of vincristine, daunorubicin, asparaginase (Erwinia), prednisone, dexrazoxane, and IT methotrexate followed by post-induction therapy with prednisone, asparaginase (Erwinia), cytarabine, methotrexate, vincristine, 6-thioguanine, cyclophosphamide, daunorubicin, and IT methotrexate, with a best response of PR from December 2001 to May 2003.

- July 2002 - an allogenic PBSCT followed by another allogenic PBSCT on 01 August 2002 conditioned with busulfan, melphalan, and fludarabine, with successful engraftment on 11 August 2002.

- May 2003 to June 2003 – 1 cycle of vincristine with a best response of treatment failure.

He entered the study on 02 July 2003 with 37% bone marrow blasts and received 5 cycles of clofarabine from 07 July 2003 to 07 November 2003. He received 2 cycles of clofarabine 52 mg/m^2/day from 07 July 2003 to 08 August 2003. His dose was reduced to 35 mg/m^2/day for Cycle 3 due to prolonged myelosuppression (on 18 August 2003: grade 4 ANC 0.2×10^9/L, grade 4 WBC 0.50×10^9/L, grade 3 platelets 19.0×10^9/L). His dose was further reduced to 26 mg/m^2/day beginning with the first dose of Cycle 4 due to prolonged myelosuppression (on 22 September 2003: grade 4 ANC 0.1×10^9/L, grade 4 WBC 0.60×10^9/L, grade 3 platelets 10.0×10^9/L). According to the investigator, he achieved a PR on 24 July 2003 (after Cycle 1), which improved to a CR on 27 August 2003 (after Cycle 2) with 1% blasts and a hypocellular marrow. The IRRP confirmed the CR. He was still on study as of 07 November 2003. In summary, this patient achieved a CR 8.3 weeks after starting treatment with clofarabine, which endured for 9.3+ weeks, and an overall survival of 17.6+ weeks. Follow-up information indicates that this patient received 3 additional cycles of clofarabine, with no further dose reduction, for a total of 8 cycles as of

last follow up on 21 February 2004. Remission has endured for 24.4+ weeks and overall survival were 32.7+ weeks.

Patient 212-018-0036 was a 9-year-old Caucasian female diagnosed with pre-B cell ALL on 12 June 1997. She received 4 prior induction chemotherapy regimens, 2 post-induction regimens, and 2 prior transplants before entering the study.

- June 1997 to October 1999 - 1 cycle of prednisone, vincristine, daunomycin, L-asparaginase, IT methotrexate, and IT cytarabine followed by post-induction therapy with cyclophosphamide, 6-mercaptopurine, cytarabine, IV methotrexate, vincristine, PEG-asparaginase, dexamethasone, doxorubicin, 6-thioguanine, prednisone, 6-mercaptopurine, PO methotrexate, and IT methotrexate, with a best response of CR from July 1997 to January 2000.

- January 2000 to May 2000 - 1 cycle of etoposide, MESNA, ifosfamide, dexamethasone, vincristine, PEG-asparaginase, IV methotrexate, IT methotrexate, IT cytarabine, and IT hydrocortisone, followed by post-induction therapy with dexamethasone, vincristine, IV methotrexate, 6-thioguanine, cytarabine, etoposide, PEG-asparaginase, ifosfamide, MESNA, idarubicin, IV methotrexate; IT methotrexate, IT cytarabine, and IT hydrocortisone, with a best response of CR from February 2000 to November 2000.

- May 2000 - an allogenic BMT conditioned with cyclophosphamide and TBI; engraftment information was not available.

- November 2000 to January 2001 - 1 cycle of vinorelbine, topotecan, thiotepa, gemcitabine, and dexamethasone, with a best response of treatment failure.

- January 2001 to February 2001 - 1 cycle of idarubicin and 2 cycles of cytarabine, with a best response of CR from February 2001 to August 2003.

- March 2001 - an allogenic BMT conditioned with busulfan and melphalan; engraftment information was not available.

She entered the study on 30 August 2003 with 80% bone marrow blasts and received 2 cycles of clofarabine 52 mg/m^2/day from 30 August 2003 to 03 October 2003. She achieved a CR on 29 September 2003 (after Cycle 1) according the investigator with 1% bone marrow blasts, which was confirmed by the IRRP. Her most recent assessment by the investigator on 04 November 2003 showed that she had a CRp (platelets = 55.0×10^9/L). She was still on study as of 21 November 2003. In summary, this patient achieved a CR 3.7 weeks after

starting treatment with clofarabine, which endured for 1.1+ weeks, and an overall survival of 4.9+ weeks. This patient received another cycle of clofarabine for a total of 3 cycles ending on 09 November 2003. She was removed from the study on 17 December 2003 due to disease progression. She was alive at last follow up on 15 March 2004. Remission has endured for 11.7 weeks, and overall survival was 28.3+ weeks.

Complete Remission in the Absence of Total Platelet Recovery

Patient 212-009-0024 was a 2-year-old Caucasian male diagnosed with pre-B cell ALL [t(1:19)] on 20 June 2002. He received 2 prior induction chemotherapy regimens, 1 post-induction therapy, and 1 prior transplant before entering the study.

- June 2002 to August 2002 - 1 cycle of dexamethasone, vincristine, L-asparaginase, prednisone, daunorubicin, and IT methotrexate, with a best response of treatment failure.
- August 2002 to September 2002 - 1 cycle of cyclophosphamide, 6-mercaptopurine, and cytarabine followed by post-induction therapy with methotrexate, 6-mercaptopurine, IT methotrexate, and IT cytarabine, with a best response of CR from September 2002 to December 2002.
- October 2002 - a BMT from a matched unrelated donor (MUD) conditioned with cyclophosphamide and TBI, with successful engraftment on 15 October 2002.

He entered the study on 30 December 2002 with 35% bone marrow blasts and received 3 cycles of clofarabine from 30 December 2002 to 03 March 2003. He achieved a CRp (platelets = 26.0×10^9/L) on 21 January 2003 (after Cycle 1) according to the investigator with 4% bone marrow blasts, which was confirmed by the IRRP. He was discontinued from the study by the investigator on 12 May 2003 to receive a stem cell reinfusion for marrow aplasia. He had an allogenic BMT on 19 May 2003, and received IT cytarabine on 23 June 2003, and IT cytarabine plus methotrexate on 22 July 2003. He was diagnosed with disease progression at the last follow up on 15 September 2003. In summary, this patient achieved a CRp 8.4 weeks after starting treatment with clofarabine, which endured for 28.6 weeks, and an overall survival of 37.0+ weeks. It should be noted, that this patient was

in remission longer with clofarabine than following transplant in October 2002. This patient was alive at last follow up on 16 March 2004. Remission has endured for 28.6 weeks, post-transplant survival was 43.1+ weeks, and overall survival was 63.1+ weeks.

Patient 212-012-0014 was a 12-year-old Black male diagnosed with pre-B cell ALL on 24 September 1999. He received 6 prior induction chemotherapy regimens and 1 post-induction regimen.

- September 1999 to April 2002 - 1 cycle vincristine, prednisone, L-asparaginase, IT cytarabine, and IT methotrexate, with post-induction therapy with vincristine, methotrexate, L-asparaginase, cyclophosphamide, dexamethasone, 6-thioguanine, cytarabine, 6-mercaptopurine, prednisone, doxorubicin, and IT methotrexate, with a best response of CR from October 1999 to April 2002.
- April 2002 to May 2002 - 1 cycle of vincristine, prednisone, L-asparaginase, daunomycin, IT cytarabine, IT methotrexate, and IT hydrocortisone, with a best response of treatment failure.
- May 2002 - 1 cycle of cytarabine, etoposide, and L-asparaginase, with a best response of treatment failure.
- June 2002 - 1 cycle of vincristine, methotrexate, IT methotrexate, IT cytarabine, and IT hydrocortisone with a best response of treatment failure.
- June 2002 to August 2002 - 2 cycles of dexamethasone, cyclophosphamide, etoposide, IT methotrexate, IT hydrocortisone, and IT cytarabine, with a best response of treatment failure.
- August 2002 to September 2002 - 1 cycle of vincristine, idarubicin, dexamethasone, L-asparaginase, IT methotrexate, IT cytarabine, and IT hydrocortisone, with a best response of treatment failure.

He entered the study on 02 October 2002 with 93% bone marrow blasts and received 2 cycles of clofarabine from 03 October 2002 to 03 November 2002. He achieved a CRp (platelets = 33.0×10^9/L) on 29 October 2002 (after Cycle 1) according to the investigator with 0% bone marrow blasts, which was confirmed by the IRRP. He was discontinued from the study by the investigator on 02 December 2002 to receive a transplant, and received cyclophosphamide, antithymocyte globulin, and MESNA as preparative chemotherapy from 07 December 2002 to 09 December 2002. He received a cord blood transplant from an

unrelated matched donor on 10 December 2002, with successful engraftment on 10 January 2003. The patient died on 24 July 2003 due to post transplantation lymphoproliferative disorder. In summary, this patient achieved a CRp 3.7 weeks after starting treatment with clofarabine, which endured for 23.1+ weeks, and an overall survival of 42.0 weeks.

Patient 212-014-0040 was a 20-year-old Hispanic male diagnosed with T cell of ALL on 05 June 2003. He was refractory to 3 consecutive regimens.

- June 2003 to September 2003 - 1 cycle of vincristine, prednisone, cyclophosphamide, high-dose methotrexate, with a best response of treatment failure.
- June 2003 - 1 cycle of cytarabine, mitoxantrone, etoposide, and dexrazoxane, with a best response of treatment failure.
- September 2003 - 1 cycle of prednisone and PEG-asparaginase, with a best response of treatment failure. One cycle of methotrexate intra-ommaya.

He entered the study on 02 October 2003 with 90% bone marrow blasts and received 2 cycles of clofarabine from 02 October 2003 to 14 November 2003. He achieved a CRp (platelets = 10.0×10^9/L) on 03 November 2003 (after Cycle 1) according to the investigator with 3% bone marrow blasts, which was confirmed by the IRRP. He was still in remission and still on study at the time of his last follow up (14 November 2003). In summary, this patient achieved a CRp 4.6 weeks after starting treatment with clofarabine, which endured for 1.6+ weeks, and an overall survival of 6.1+ weeks. This patient was removed from the study due to his death on 05 December 2003 as a result of hand/foot syndrome/ multiorgan failure 21 days after receiving his last dose of clofarabine. Per follow up, the remission endured for 4.6 weeks and overall survival was 9.1 weeks.

Partial Responders

Patient 212-004-0025 was a 3-year-old Hispanic male diagnosed with B-cell ALL (Philadelphia positive) [t(9:22)] on 17 May 2001. He received 4 prior induction chemotherapy regimens, 2 post-induction regimens, and 1 prior transplant.

- May 2001 to October 2001 - 1 cycle of prednisone, vincristine, daunomycin, L-asparaginase, IT methotrexate, and IT cytarabine followed by post-induction therapy with cyclophosphamide, cytarabine, 6-mercaptopurine, vincristine, asparaginase, IV methotrexate, and IT methotrexate, with a best response of CR from June 2001 to April 2002.

- December 2001 - a cord blood transplant from an unrelated donor (4/6 antigen match), conditioned with busulfan and cyclophosphamide, with successful engraftment on 22 March 2002.

- April 2002 to October 2002 - 1 cycle of imatinib mesylate, dexamethasone, vincristine, PEG-asparaginase, IT methotrexate, IT cytarabine, and IT hydrocortisone followed by post-induction therapy with imatinib mesylate, IT methotrexate, IT cytarabine, and IT hydrocortisone, with a best response of CR from June 2002 to October 2002.

- October 2002 to December 2002 - 1 cycle of vincristine, PEG-asparaginase, imatinib mesylate, dexamethasone, IT methotrexate, IT cytarabine, and IT hydrocortisone, with a best response of treatment failure.

- December 2002 to January 2003 - 1 cycle of etoposide, ifosfamide, MESNA, IT methotrexate, IT cytarabine, and IT hydrocortisone, with a best response of treatment failure.

He entered the study on 09 January 2003 with 66% bone marrow blasts and received 4 cycles of clofarabine from 09 January 2003 to 04 April 2003. The investigator considered this patient to be a treatment failure; however, the IRRP considered him to have achieved a PR on 05 February 2003 (after Cycle 1), with (03 February 2003) 16% bone marrow blasts and a normocellular marrow. He was discontinued from the study on 23 April 2003 by the investigator due to failure to achieve a response, and died on 16 May 2003 due to malignant disease. In summary, this patient achieved a PR (according to the IRRP) 3.9 weeks after starting treatment with clofarabine, which endured for 2.7 weeks, and an overall survival of 18.1 weeks.

Patient 212-006-0003 was an 8-year-old Caucasian female diagnosed with pre-B cell ALL on 25 September 2000. She received 4 prior induction chemotherapy regimens and 1 post-induction regimen.

- September 2000 to April 2002 - 1 cycle of dexamethasone, vincristine, PEG-asparaginase, IT cytarabine, and IT methotrexate followed by post-induction therapy with vincristine, 6-mercaptopurine, IV methotrexate, doxorubicin, dexamethasone, PEG-asparaginase, cyclophosphamide, cytarabine, methotrexate PO, IT methotrexate, and IT cytarabine, with a best response of CR from October 2000 to May 2002.

- May 2002 to June 2002 - 1 cycle of prednisone, vincristine, daunomycin, L-asparaginase, IT cytarabine, and IT hydrocortisone, with a best response of CR from 11 June 2002 to 19 June 2002.

- June 2002 to July 2002 - 1 cycle of etoposide, ifosfamide, MESNA, dexamethasone, and vincristine with a best response of CR.

- July 2002 - 1 cycle of vincristine, cytarabine, 6-thioguanine, and prednisone, but was not evaluable.

She entered the study on 22 July 2002 with 67% bone marrow blasts and received 3 cycles of clofarabine from 22 July 2002 to 25 August 2002. She achieved a PR on 19 August 2002 (after Cycle 2) according to the investigator with 12% bone marrow blasts, which was confirmed by the IRRP. She was discontinued from the study on 04 September 2002 due to disease progression and died on 02 April 2003 from malignant disease. No autopsy was performed. In summary, this patient achieved a PR 4.0 weeks after starting treatment with clofarabine, which endured for 2.3 weeks, and an overall survival of 36.3 weeks.

Patient 212-006-0004 was a 15-year-old Arab female diagnosed with pre-B cell ALL (Philadelphia positive) [t(9:22)] on 23 August 2001. She received 3 prior induction chemotherapy regimens, 2 post-induction regimens, and 1 prior transplant.

- August 2001 - 1 dose of vincristine and idarubicin, but was not evaluable.

- August 2001 to January 2002 - 1 cycle of vincristine, daunomycin, L-asparaginase, prednisone, IT cytarabine, and IT methotrexate followed by post-induction therapy with prednisone, cyclophosphamide, 6-mercaptopurine, IV cytarabine, vincristine, L-asparaginase, IV methotrexate, IT methotrexate, IT cytarabine, and IT hydrocortisone, with a best response of CR from September 2001 to April 2002.

- February 2002 - an allogenic BMT conditioned with fludarabine, melphalan, and TBI with successful engraftment on 04 March 2002.

- April 2002 to August 2002 - 1 cycle of imatinib mesylate, hydroxyurea, vincristine, dexamethasone, L-asparaginase, and IT methotrexate, with a best response of CR from May 2002 to July 2002.

- May 2002 - stem cell infusion.

- 15 May 2002 to 02 August 2002 - post-induction therapy with imatinib mesylate and IT cytarabine.

She entered the study on 02 August 2002 with 34% bone marrow blasts and received 2 cycles of clofarabine. Per investigator's clinical judgment, the aggressive nature of the patient's highly resistant disease warranted moving forward with clofarabine treatment immediately. She received 52 mg/m^2/day clofarabine from 02 August 2002 to 06 August 2002 (Cycle 1) and 4 doses of Cycle 2 from 26 August 2002 to 29 August 2002. She was considered a treatment failure by the investigator; however, the IRRP considered her to have achieved a PR on 16 August 2002 (after Cycle 1) with 3% bone marrow blasts and a hypocellular marrow. She died on 20 September 2002 due to sepsis NOS that started on Day 5 of Cycle 2 (30 August 2002). The sepsis was considered to be secondary to her disease and no autopsy was performed. In summary, this patient achieved a PR 2.0 weeks after starting treatment with clofarabine, which endured for 1.0 week, and an overall survival of 7.0 weeks.

Patient 212-010-0042 was an 18-year-old Brazilian male (ethnicity unknown) diagnosed with ALL on 27 April 1999. He received 2 prior induction chemotherapy regimens and 1 post-induction regimen before entering this study.

- May 1999 to November 2001 – 1 induction regimen of daunoblastin, vincristine, dexamethasone, L-asparaginase, and methotrexate with IT methotrexate, cytarabine, and dexamethasone followed by vincristine, L-asparaginase, cytarabine, methotrexate and 6-mercaptopurine with IT methotrexate, cytarabine, and dexamethasone for a best response of CR.

- July 2003 to August 2003 – 1 induction regimen of cyclophosphamide, dexamethasone, vincristine, doxorubicin, methotrexate, leucovorin, and cytarabine with IT methotrexate and cytarabine for a best response of PR.

The patient entered this study on 06 November 2003 with 81% bone marrow blasts and received 2 cycles of clofarabine 52 mg/m^2/day from 06 November 2003 to

01 December 2003. He achieved a PR according to the investigator on 19 November 2003 (blasts 15%, Cycle 1), which was confirmed by the IRRP (start date 12 December 2003 due to number of cells counted = 200). The patient was removed from the study on 12 December 2003 to receive a BMT. The patient underwent an allogenic peripheral blood BMT on 23 December 2003 that was successfully engrafted on 03 January 2004. Bone marrow blasts were 0.5% on 13 January 2004 and the patient was alive as of last follow up on 14 April 2004. In summary, this patient achieved a PR 5.1 weeks after starting treatment with clofarabine, which endured 4.6+ weeks. Post-transplant survival was 16.1+ weeks, and overall survival was 22.9+ weeks.

Patient 212-014-0007 was a 6-year-old Caucasian male diagnosed with pre-B cell ALL on 15 September 1999. He received 3 prior induction chemotherapy regimens, 1 post-induction regimen, and 1 prior transplant.

- September 1999 to August 2001 - 1 cycle of vincristine, prednisone, cyclophosphamide, daunomycin, PEG-L-asparaginase followed by post-induction therapy with cytarabine, vincristine, etoposide, 6-thioguanine, prednisone, PEG-L-asparaginase, methotrexate, daunomycin, doxorubicin, 6-mercaptopurine, PO methotrexate and IT methotrexate, with a best response of CR from 1999 to January 2002.

- January 2002 - 1 cycle of vincristine, daunorubicin, and dexamethasone, with a best response of treatment failure.

- January 2002 to March 2002 - 1 cycle of L-asparaginase and 2 cycles of cytarabine, with a best response of CR from January 2002 to August 2002.

- May 2002 - an allogenic PBSCT conditioned with thiotepa, cyclophosphamide, and TBI, with successful engraftment on 28 May 2002.

He entered the study on 29 August 2002 with 56% bone marrow blasts and received 2 cycles of clofarabine from 29 August 2002 to 30 September 2002. He achieved a PR on 19 September 2002 (after Cycle 1) with 15% bone marrow blasts and a hypocellular marrow, which was confirmed by the IRRP. He was discontinued from the study on 16 October 2002 by the investigator to receive a stem cell transfusion for marrow aplasia. He received an allogenic BMT on 16 October 2002 with successful engraftment on 20 November 2002.

He died on 25 March 2003 from diffuse large B-cell lymphoma per his autopsy results. In summary, this patient achieved a PR 3.0 weeks after starting treatment with clofarabine, which endured for 7.6 weeks, and an overall survival of 29.7 weeks.

PR by Investigator, NE by IRRP

Patient 212-014-0029 was a 12-year-old Caucasian male diagnosed with pre-B cell ALL on 18 April 2002. He received 3 prior induction chemotherapy regimens and 1 prior transplant.

- April 2002 to May 2002 – 1 cycle of prednisone, vincristine, daunomycin, L-asparaginase, IT methotrexate, and IT cytarabine, with a best response of treatment failure.
- May 2002 to June 2002 - 1 cycle of asparaginase, methotrexate, vincristine, cytarabine, IT cytarabine, and IT methotrexate, with a best response of PR.
- June 2002 to August 2002 – 2 cycles of topotecan, vinorelbine, thiotepa, and IT methotrexate, with a best response of CR from August 2002 to June 2003.
- 17 September 2002 – a PBSCT from an unrelated matched donor conditioned with cyclophosphamide and TBI, with successful engraftment on 07 October 2002.

He entered the study on 16 June 2003 with 93% blasts and received 2 cycles of clofarabine from 16 June 2003 to 07 July 2003. According to the investigator, the patient achieved a PR on 23 July 2003 (after Cycle 2); however, the IRRP did not consider this patient to be evaluable because of the poor quality of the bone marrow sample. He was discontinued from the study by the investigator on 24 July 2003 to receive a transplant. He received a PBSCT from an unrelated matched donor on 28 August 2003, engraftment unknown. He was still alive at the last follow up on 07 October 2003. In summary, this patient experienced a PR at 2.4 weeks after starting treatment with clofarabine, post-transplant survival of 5.7+ weeks, and an overall survival of 16+ weeks. This patient was alive at last follow up on 23 March 2004, with a post-transplant survival of 29.7+ weeks, and overall survival of 40.1+ weeks.

9.2. Responder Narratives from CLO-222

The narratives provided in this appendix, include the original narratives submitted to the FDA in March, along with an updated section at the end of some narratives that contains new data received for the 120-day update.

Complete Remission

There were no patients confirmed as CR by the IRRP.

Complete Remission Without Platelet Recovery

Patient 222-014-0003 was a 4-year-old Asian male who was diagnosed with AML on 26 May 2000. He received 5 prior induction chemotherapy regimens, 1 post-induction regimen, and 1 prior transplant before entering the study:

- February 2000 to May 2000 - 1 induction regimen of prednisone, vincristine, L-asparaginase, 6-mercaptopurine, PO methotrexate, IT methotrexate, IT hydrocortisone, and IT cytarabine. A response assessment was not available.
- May 2000 to December 2000 - 1 induction regimen of etoposide, daunorubicin, cytarabine, 6-thioguanine, and IT cytarabine, with a response of CR; August 2000 to December 2000 followed by post-induction therapy with cytarabine, L-asparaginase, vincristine sulfate, cytarabine, cyclophosphamide, etoposide, 6-thioguanine, and IT cytarabine.
- May 2001 to July 2001 – cytarabine, L-asparaginase, and IT cytarabine with a response of treatment failure.
- July 2001 to October 2001 - 1 induction regimen of topotecan, vinorelbine tartrate, thiotepa, and gemcitabine with a response of treatment failure
- October 2001 to December 2001 - 1 induction regimen of cytarabine, idarubicin, and cytarabine with a response of CR.
- February 2002 - an allogenic PBSCT, conditioned with fludarabine, thiotepa, and TBI, with successful engraftment on 28 February 2002.

He entered the study on 11 July 2002 with 28% bone marrow blasts and received 5 cycles of clofarabine from 15 July 2002 to 20 December 2002. The patient received 52 mg/m^2/day

clofarabine during Cycles 1 and 2 from 15 July 2002 to 17 August 2002. The patient experienced dose reductions between 3 cycles of clofarabine due to febrile neutropenia. His dose was reduced to 35 mg/m^2/day for Cycle 3; to 26 mg/m^2/day for Cycle 4; and to 15 mg/m^2/day for Cycle 5. He achieved a CRp according to the investigator on 08 August 2002 (at the beginning of Cycle 2) with 1% bone marrow blasts, which was confirmed by the IRRP on 24 September 2002. The IRRP's response assessment for this patient confirmed CRp. He went off study on 27 January 2003 and was scheduled for transplant. On 11 February 2003 he received an allogenic PBSCT with successful engraftment on 10 March 2003. He was still alive at the last follow up on 04 November 2003. In summary, this patient achieved a CRp 4.1 weeks after starting treatment with clofarabine, which has endured for 64.0+ weeks with a progression-free survival of 68.1+ weeks, and an overall survival of 68.1+ weeks.

This patient was alive as of last follow up on 30 April 2004. In summary, his duration of remission changed to 73.4+ weeks, post-transplant survival was 63.4+ weeks, and overall survival was 93.6+ weeks.

Partial Remission

Patient 222-006-0013 was a 10-year-old Hispanic male who was diagnosed with M1 AML on May 2002 (exact date not given). He received 4 prior induction regimens before entering the study:

- May 2002 - 1 induction regimen of daunorubicin and cytarabine with an unevaluable response;
- July 2002 - 1 induction regimen of cytarabine, etoposide, and cyclophosphamide with a response of treatment failure;
- August 2002 - 1 induction regimen of mitoxantrone and cytarabine with an unevaluable response;
- October 2002 - 1 induction regimen of dexamethasone and 6-mercaptopurine with a response of treatment failure.

He entered the study on 04 November 2002 with 75% bone marrow blasts and received 3 cycles of clofarabine 52 mg/m^2/day from 04 November 2002 to 26 December 2002. He did not receive Day 5 dose (Cycle 3) due to septic shock. He died on 28 December 2002. According to the investigator he achieved a PR on 16 December 2002 with 20% bone marrow blasts, which was confirmed by the IRRP. Time to remission was 6 weeks, duration of remission was 1.7 weeks, and survival was 7.7 weeks.

Patient 222-006-0036 was a 5-year-old Caucasian male diagnosed with AML (JMML), subtype unknown, on 16 April 2001. He received 3 prior induction chemotherapy regimens and 2 post induction chemotherapy regimens before entering the study.

- April 2001 to June 2001 - 1 induction regimen of cytarabine, fludarabine, and cis-retinoic acid followed by cis-retinoic acid per cooperative group protocol AAML 0122. His best response to this regimen was not documented.
- June 2001 - prepared for a BMT with etoposide cytarabine, cyclophosphamide, IT cytarabine, and TBI. On 19 June 2001 he received TBI, followed by an allogenic BMT that successfully engrafted on 13 July 2001 and was complicated by grade 1 GVHD.
- June 2002 – prepared for a second transplant with cis-retinoic acid, etoposide, fludarabine, melphalan and radiation to Waldeyer's ring. He received a peripheral blood allogenic transplant on 17 June 2002 that engrafted on 09 July 2002.
- October 2003 to November 2003 – 1 induction regimen of interleukin-2 followed by interleukin-2 and cis-retinoic acid with a best response of treatment failure.
- November 2003 to December 2003 - 1 induction regimen of tipifamib with a best response of treatment failure.

He entered this study on 05 January 2004 with 59% blasts and received 3 cycles of clofarabine 52 mg/m^2/day from 06 January 2004 to 05 March 2004. He achieved a PR according to the investigator on 22 March 2004 (Cycle 3) with 6% blasts, which was confirmed by the IRRP. He was discontinued from the study on 29 March 2004 to undergo a transplant. In summary, this patient achieved a PR 10.9 weeks after starting treatment with clofarabine, which endured 5.6+ weeks with an overall survival of 16.4+ weeks.

ILEX's update resulted in some changes to the previously reported data. ILEX learned that this patient underwent an unrelated donor stem cell transplant on 22 April 2004, and his post-transplant marrow blood showed 100% donor chimerism, although there were no aspirate data available by the data cutoff time. In summary, this patient's PR occurring 10.9 weeks after beginning clofarabine treatment remained unchanged; however, the remission has endured for 5.6+ weeks, post-transplant survival was 1.1+ weeks, and overall survival was 16.4+ weeks.

Patient 222-009-0018 was a 12-year-old biracial (Black/Caucasian) female who was diagnosed with M2 AML on 09 October 2002. She received 1 prior induction chemotherapy regimen before beginning treatment with clofarabine.

- October 2002 to December 2002 - 1 induction regimen of cytarabine, 6-thioguanine, daunomycin, and IT cytarabine with a response of CR.

She enrolled in the study on 06 February 2003 with 56% bone marrow blasts and received 2 cycles of clofarabine 52 mg/m^2/day from 07 February 2003 to 15 March 2003. She achieved a PR on 11 March 2003 according to the investigator with 5% bone marrow blasts with a hypocellular marrow, which was confirmed by the IRRP. She relapsed on 14 April 2003 and went off study with disease progression. She went on to alternative treatment on 15 April 2003 and underwent a transplant in May 2003. She died on 27 July 2003 secondary to GVHD. Her time to remission was 4.6 weeks, which endured for 4.9 weeks with overall survival of 24.3 weeks.

Patient 222-014-0002 was a 15-year-old Caucasian male who was diagnosed with M1 AML on 09 August 1995. He received 5 prior induction chemotherapy regimens, 4 post-induction chemotherapy regimens, and 1 prior PBSCT before receiving treatment with clofarabine.

- 1995 to 1997 (exact dates unknown) - 1 induction with AML-BFM-93, with a response of CR; followed by a post-induction treatment (exact dates and drugs unknown)

- October 1997 to January 2000 (exact dates unknown) - 1 induction regimen with AML-RE2-BFM97, with a response of CR; 1 post-induction treatment regimen (exact dates and drugs unknown)

- In 2000 (exact dates unknown) – 1 induction regimen with AML-RE2-BFM97, with a response of CR; 1 post-induction regimen with AML-RE2-BFM97

- July 2001 to September 2001 - 1 induction regimen with daunorubicin and cytarabine with a response of CR

- September 2001 to October 2001 - 1 induction regimen with AML-RE2-BFM97 with an unevaluable response; followed by 1 post-induction treatment regimen in September 2001 with 6-thioguanine and cytarabine

- December 2001 – received a PBSCT, conditioned with thiotepa and fludarabine, with successful engraftment on 15 December 2001.

He enrolled in the study on 28 June 2002 with 95% bone marrow blasts and received 2 cycles of clofarabine 52 mg/m^2/day from 28 June 2002 to 23 July 2002. Dose 4 of Cycle 2 was interrupted due to the patient's sensation of heaviness. He achieved a PR on 19 July 2002 according to the IRRP, although the quality of the specimen was not good (marrow was hypocellular with 19% blasts, but no erythroid precursors). The date of confirmation was unknown. According to the investigator's assessment the patient achieved a PR on 27 August 2002. The patient went off study at investigator's decision due to aplastic marrow on 27 August 2002 to receive a transplant. He received 2 transplants post-treatment with clofarabine. The first PBSCT occurred on 27 August 2002, was not successful, and was repeated on 30 August 2002. No information was available regarding the outcome of the engraftment. The patient died on 26 January 2003 due to progressive pneumonia. No autopsy was performed. In summary, this patient's time to remission was 3 weeks; duration of remission was 20.0 weeks, and overall survival was 30.3 weeks. His post-transplant survival was 21.3 weeks.

Patient 222-014-0019 was a 21-year-old Caucasian female at time of initial diagnosis with M2 AML (trisomy 21) on 16 April 2002. She received 1 prior induction chemotherapy regimen, 1 post-induction chemotherapy regimen, and 1 prior transplant before being treated with clofarabine.

- April 2002 to July 2002 - 1 induction regimen with etoposide, daunorubicin, cytarabine, 6-thioguanine, and IT cytarabine with a CR; followed by 1 post-induction regimen with 6-thioguanine, etoposide, daunorubicin, cytarabine, asparaginase, and IT cytarabine.

- August 2002 - a PBSCT conditioned with thiotepa and fludarabine, with successful engraftment on 24 August 2002

She enrolled in the study on 14 February 2003 with 73% bone marrow blasts and received 2 cycles of clofarabine 52 mg/m^2/day from 18 February 2003 to 09 March 2003. On 24 March 2003, she achieved a PR by the investigator with 5% bone marrow blasts and a hypocellular marrow, which was confirmed by the IRRP. On 28 March 2003 she went off study due to aplastic marrow at the investigator's decision. She received a PBSCT post-clofarabine treatment on 03 April 2003 with successful engraftment on 29 April 2003. She died on 18 November 2003 due to cardiopulmonary arrest. It is unknown if an autopsy was performed. In summary, she achieved a PR 4.9 weeks after beginning treatment with clofarabine, which endured for 12.4 weeks, with an overall survival of 39.0 weeks.

Patient 222-014-0027 was a 3-year-old Caucasian male who was diagnosed with M2 AML (trisomy 8) on 29 April 2003. He received 2 prior induction chemotherapy regimens before treatment with clofarabine.

- May 2003 to June 2003 – 1 induction regimen with cytarabine, daunorubicin, etoposide, and IT cytarabine; with a response of treatment failure

- June 2003 to August 2003 – 1 induction regimen with cytarabine and L-asparaginase with a response of PR

He enrolled in the study on 12 September 2003 with 52% bone marrow blasts and received 3 cycles of clofarabine 52 mg/m^2/day from 15 September 2003 to 07 November 2003. On 20 October 2003 he achieved a PR by the investigator's assessment with 13% bone marrow blasts, which was confirmed by the IRRP on 27 October 2003. He relapsed on 03 November 2003.

In summary, he achieved a PR 5 weeks after starting treatment with clofarabine, which endured for 2.6 weeks and an overall survival of 7.6+ weeks. No follow-up information was

provided, but the patient was still alive and on study as of the 21 November 2003 data cutoff date.

ILEX's update resulted in some changes to the previously reported data. This patient received Cycle 4 of 52 mg/m^2/day clofarabine from 17 November 2003 to 21 November 2003, and then underwent a peripheral blood stem cell transplant on 12 December 2003 after conditioning with busulfan, melphalan, and equine ATG, and was successfully engrafted on 30 December 2003 with 3% blasts on 07 January 2004. He was still alive at last follow up on 05 April 2004. His remission endured for 2.0 weeks, post-transplant survival was 16.4+ weeks, and overall survival was 29.0+ weeks.

Patient 222-014-0031 was a 4-year-old Caucasian female diagnosed with AML (subtype M0) on 03 September 2003.

She received 2 prior induction chemotherapy regimens before entering this study:

(1) 05 September 2003 to 11 September 2003- 1 induction regimen of cytarabine, daunorubicin, 6-thioguanine, and IT cytarabine with a best response of treatment failure.

(2) 22 September 2003 to 27 September 2003 – 1 induction regimen of cytarabine, mitoxantrone, and IT cytarabine with a best response of PR.

She entered this study on 15 October 2003 and received 2 cycles of 52 mg/m^2/day clofarabine from 15 October to 19 October 2003 (Cycle 1) and 04 November to 08 November 2003 (Cycle 2). She achieved a PR according to the investigator with 0% blasts in marrow on 24 November 2003, which was confirmed by the IRRP with 4% blasts in marrow (Appendix E, CLO-222, Listing 16.2.6.1.1) on 05 December 2003. She was discontinued from the study on 09 December 2003 to undergo an allogenic BMT, which occurred on 17 December 2003 with successful engraftment (1% blasts) on 05 January 2004. This patient was still alive as of last follow up on 06 April 2004. In summary, the time to remission after starting treatment with clofarabine was 5.7 weeks, which has endured for 7.6+ weeks. Post-transplant survival was 15.9+ weeks, and overall survival was 24.9+ weeks.

Patient 222-015-0017 was an 11-year-old Caucasian male who was diagnosed with M4 AML on 01 March 2002.

He received 2 prior induction chemotherapy regimens, and 1 prior post-induction chemotherapy regimen before starting treatment with clofarabine.

- March 2002 to July 2002 – 1 induction regimen with daunorubicin, cytarabine, and 6-thioguanine with a response of CR; followed by 1 post induction regimen with etoposide, mitoxantrone, cyclosporine, and IT cytarabine.
- November 2002 - 1 induction regimen with cladribine and idarubicin; with a response of treatment failure

He enrolled in the study on 02 January 2003 with 52% bone marrow blasts and received 1 cycle of clofarabine 52 mg/m^2/day from 03 January 2003 to 07 January 2003. On 28 February 2003 the investigator assessed his response as PR with 0% bone marrow blasts (on 13 February 2003), which was confirmed by the IRRP on 21 February 2003. He went off study 28 February 2003 to receive a transplant. On 13 March 2003 he received a cord blood MUD transplant, which successfully engrafted (date of engraftment unknown). He was still alive at the last follow up on 16 October 2003. In summary, the patient achieved a PR 5.9 weeks after starting treatment with clofarabine, which endured for 35.0+ weeks, with overall survival of 40.9+ weeks.

As of last follow up on 22 April 2004, this patient's remission had endured for 56.6+ weeks, post-transplant survival was 58.0+ weeks, and overall survival was 67.9+ weeks.

Investigator-Assessed Complete Remission

Patient 222-014-0034 was a 21-year-old Caucasian male diagnosed with AML (subtype unknown) on 20 October 2000. This patient was noted to have the MLL gene abnormality.

He received 3 prior induction chemotherapy regimens and 1 transplant before enrolling in this study:

(1) 21 October 2000 to 2001 – 1 induction regimen with idarubicin, daunorubicin, cytarabine, IT cytarabine, VP-16, dexamethasone, 6-thioguanine, and G-CSF according to CCG protocol 296, Regimen A. His best response was CR.

(2) 19 December 2002 – peripheral blood MUD (10/10) transplant, with successful engraftment on 27 January 2003.

(3) 19 February 2001 to 05 April 2001 – unknown regimen according to the Capezzi cooperative group, protocol, for a best response of NE.

(4) 22 September 2002 to 29 October 2002 – cytarabine, L-asparaginase, and IT cytarabine, for a best response of CR.

He enrolled in the study on 18 November 2003 with 12% blasts, and underwent 4 cycles: 52 mg/m^2/day clofarabine from 19 November 2003 to 23 November 2003 (Cycle 1) and 15 December 2003 to 19 December 2003 (Cycle 2), 26 mg/m^2/day clofarabine from 19 January 2004 to 23 January 2004 (Cycle 3), and 15 mg/m^2/day clofarabine from 08 March 2004 to 12 March 2004 (Cycle 4). On 12 December 2003 the investigator assessed the patient's response as CR; however, on 15 December 2003, the IRRP assessed the patient's response as NE due to only 12% blasts at study entry. The patient remains on study with an overall survival of 23.3+ weeks. In addition, ILEX learned that this patient underwent a transplant on 26 May 2004, after the data cutoff time.

Investigator-Assessed Partial Remissions

Three patients were determined by the investigators to be PRs; however these responses were not confirmed by the IRRP for the reasons stated in the brief narratives below.

Patient 222-006-0014 was an 11-year-old Hispanic female diagnosed with M2 AML on 05 October 2001.

She received 1 prior induction regimen and 1 prior post-induction chemotherapy regimen before beginning treatment with clofarabine.

- October 2001 to May 2002 – 1 induction regimen with idarubicin, cytarabine, etoposide, 6-thioguanine, dexamethasone, daunorubicin, and IT cytarabine with a CR; followed by 1 post-induction chemotherapy regimen with idarubicin, cytarabine, etoposide, 6-thioguanine, dexamethasone, daunorubicin, fludarabine, L-asparaginase, and IT cytarabine.

She enrolled in the study on 11 November 2002 with 20% bone marrow blasts and received 2 cycles of 52 mg/m^2/day clofarabine from 12 November 2002 to 08 December 2002. She achieved a response of PR on 03 December 2002 according to the investigator with 9% bone marrow blasts. The IRRP considered this patient not evaluable because she enrolled with 20% blasts in her marrow (an M2 marrow) and questioned her eligibility for enrollment in the study. She went off study on 15 January 2003 because she was scheduled for a transplant. On 27 January 2003 she received a MUD cord blood transplant with successful engraftment on 15 February 2003. At her last follow up on 04 September 2003 there was no disease progression. She has survived 31.4+ weeks post transplant.

At this patient's last follow up on 22 April 2004, her post-transplant survival was 64.4+ weeks and overall survival was 75.3+ weeks.

Patient 222-010-0020 was an 18-year-old Caucasian male who was diagnosed with M4 AML on 30 June 2002.

He received 5 prior induction and 1 post induction chemotherapy regimen prior to treatment with clofarabine:

- June 2002 to July 2002 – 1 induction regimen with idarubicin, cytarabine, etoposide, 6-thioguanine, dexamethasone, daunorubicin, G-CSF, and IT cytarabine with a PR; August 2002 to September 2002 - followed by a post-induction regimen with daunorubicin and IT cytarabine.
- October 2002 – 1 induction regimen with cytarabine and fludarabine; with a response of treatment failure.
- November 2002 – 1 induction regimen with mitoxantrone and cytarabine; with a response of treatment failure.
- January 2003 – he received hydroxyurea and gemtuzumab ozogamicin; with a response of treatment failure.
- February 2003 - he received topotecan, cladribine, and IT cytarabine; with a response of treatment failure.

He enrolled in the study 21 February 2003 with 98% blasts and received 2 cycles of 52 mg/m^2/day clofarabine from 22 February 2003 to 16 March 2003. According to the

investigator he achieved a PR on 07 March 2003 with 2% bone marrow blasts. The IRRP considered this patient to be a treatment failure, as the bone marrow reports dated 07 and 26 March state there was persistent involvement of bone marrow by myelomonocytic leukemia. He went off study 30 March 2003 and was scheduled to receive a transplant. On 08 April 2003, he received an allogenic PBSCT, which successfully engrafted on 02 May 2003. On 10 June 2003 he was determined to have disease progression. He died on 11 September 2003 from malignant disease. He survived 22.3 weeks post transplant.

Patient 222-014-0029 was a 20-year-old Caucasian female diagnosed with M5 AML in March 2003. Prior to treatment with clofarabine she received 3 induction regimens.

- March 2003 to April 2003 - 1 induction regimen with dexamethasone, cytarabine, 6-thioguanine, etoposide, rubidomycin, and idarubicin with a response of treatment failure.
- June 2003 - she received fludarabine, cytarabine, and G-CSF with a response of PR.
- August 2003 - she received mitoxantrone and cytarabine with a response of PR.

She experienced a relapse on 22 September 2003 and enrolled into the study with 63% bone marrow blasts. She received 1.5 cycles of 52 mg/m^2/day clofarabine from 22 September 2003 to 18 October 2003. She did not receive Day 4 and Day 5 doses (Cycle 2) due to an AE (septic shock). According to the investigator she achieved a PR on 09 October 2003. Blasts were not reported, but the marrow was aplastic. She died on 19 October 2003 (Day 4, Cycle 2) due to septic shock. She had an overall survival of 3.9 weeks. According to the IRRP, the patient was not evaluable due to early death. No autopsy was performed.

OTHER PATIENTS WHO WENT ON TO TRANSPLANT

Three patients who were not considered to be responders or who were not evaluable per investigator and/or IRRP actually received clinical benefit (substantial cytoreduction) and went on to transplant after clofarabine treatment.

Patient 222-010-0022 was a 17-year-old Caucasian male diagnosed with M4 AML on 14 April 2002. Prior to treatment with clofarabine he received 2 induction regimens, 1 post-induction regimen, and 1 prior transplant.

- April 2002 to May 2002 – he received an induction regimen with IV cytarabine, cladribine, daunomycin, etoposide, and IT methotrexate, IT cytarabine, and IT hydrocortisone with a best response of PR.
- July 2002 – he received a post-induction regimen of daunomycin, cytarabine, etoposide, and IT methotrexate, IT cytarabine, and IT hydrocortisone.
- December 2002 – he received an allogenic BMT conditioned with thiotepa, cyclophosphamide, and TBI.
- May 2003 – he received an induction regimen of cytarabine, with a response that was not evaluable.

He came on study 19 May 2003 with 37% bone marrow blasts. He received 4 of 5 doses of Cycle 1 of 52 mg/m^2/day clofarabine, beginning 21 May 2003. He did not receive the Day 5 dose due to AEs (hypotension, fever, neutropenia, SIRS, serum sickness). According to the investigator, the patient was not evaluable, and went off study with a hypoplastic marrow for transplant. He received a PBSCT in June 2003, conditioned with fludarabine, thiotepa, melphalan, and rituximab. He died on 08 November 2003 due to multi-organ failure. He had an overall survival of 24.4 weeks. According to the IRRP, this patient was not evaluable because the bone marrow showed possible persistent leukemia but the specimen was so hypocellular that this could not be confirmed. An updated safety narrative was provided in the 120-day safety update.

Patient 222-010-0023 was a 2-year-old Caucasian male diagnosed with AML (subtype unknown; monosomy 7) in May 2002. Prior to treatment with clofarabine he received 4 induction regimens (2 experimental) and 1 PBSCT.

- May 2002 - June 2002 - He received 1 induction regimen with R11577 (an investigational agent) with a response of treatment failure.
- July 2002 - He received fludarabine, and cytarabine with a response of treatment failure.

- August 2002 – He received an allogenic PBSCT, with successful engraftment in September 2002 (exact date unknown).

- March 2003 – April 2003 - He received arsenic trioxide (an investigational agent) with a response of treatment failure.

- April 2003 – June 2003 – He received etoposide with a response of treatment failure.

A patient with this variation of AML (monosomy 7) has no current therapeutic options that realistically offer any chance of prolonged survival. This is evidenced by the 4 prior attempts to treat him, 2 of which were with investigational agents. He entered CLO-222 with a waiver as he had been treated with etoposide within 2 weeks of going on study 26 June 2003. He entered the study with 68% bone marrow blasts and 14,210 absolute peripheral blood blasts. He received 1 cycle of 52 mg/m^2/day clofarabine from 26 June 2003 to 30 June 2003, with a dramatic and rapid decrease of his absolute peripheral blood blasts to 0.05 on Day 4, a reduction of >99%. As a result of this substantial cytoreduction, he was discontinued from the study on 16 July 2003 to receive transplant. On 30 July 2003 he received a PBSCT (3/6 antigen match) but developed grade 3 GVHD. As of last follow up on 17 November 2003, he was still alive, with an overall survival of 20.6+ weeks.

This patient died on 18 March 2004 due to disease progression. In summary, his post-transplant survival was 33.1 weeks, and overall survival was 38.0 weeks.

Patient 222-014-0035 was a 14-year-old Hispanic male diagnosed with AML (subtype M4) on 11 June 2003. Prior to treatment with clofarabine he received 2 prior induction chemotherapy regimens:

- 13 June 2003 to 31 October 2003 – idarubicin, cytarabine, etoposide, 6-thioguanine, dexamethasone, daunorubicin, and IT cytarabine with a best response of CR.

- 26 November 2003 to 16 December 2003 – fludarabine, cytarabine, idarubicin, and filgrastim with a best response of TF.

He enrolled in the study on 18 December 2003 with 27% blasts, and underwent 3 cycles of 52 mg/m^2/day clofarabine from 18 December 2003 to 13 February 2004. On 02 January 2004 the investigator assessed his response as PR; however, although the IRRP agreed that the patient was a PR with an M2 marrow on 06 February 2004, he still had circulating blasts and was thus assessed as a TF. The patient was taken off study on 01 March 2004 due to disease progression. His disease progressed 10.6 weeks after initiating clofarabine treatment, and the patient died on 02 April 2004, with an overall survival of 15.1 weeks.

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