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IRB Protocol

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A Phase I/II Study of Clofarabine in Patients with Relapsed T-cell and NK-Cell Lymphomas

THERAPEUTIC/DIAGNOSTIC PROTOCOL

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase I/II trial of clofarabine for the treatment of patients with relapsed or refractory mature T- and NK-cell lymphomas. Earlier and ongoing phase I and II trials established safety and anti-tumor activity of clofarabine in patients with acute leukemia and solid tumors. The only two patients with T- and NK-cell lymphoma/leukemia who were treated with clofarabine had complete responses which led to our interest in studying this agent in patients with T- and NK-cell lymphoma.

With the exception of ALK-1 expressing ALCL and certain pediatric lymphomas, T-cell lymphomas are a heterogeneous and poor prognostic subset of non-Hodgkin's lymphomas (NHL). Overall, standard chemotherapy regimens achieve complete responses in about 40% of patients and produce 2- and 5-year survival rates of 20 – 30% [1-3]. In more specific analyses, outcomes for patients with intermediate or poor prognosis based upon the international prognostic index (IPI) have a 0 - 23% survival at five years and a 0 - 10% failure-free survival with no plateau on the curves suggesting that very few of these patients are cured of their disease [2-4]**.**

The long-term goal of this research is to improve outcomes for these patients by identifying new agents with activity against T-cell lymphomas in the hope of generating more effective treatment regimens. The primary objective of this study is to evaluate the utility of clofarabine in the treatment of T- and NK- cell lymphoma by defining the maximum tolerated dose (MTD) and the dose limiting toxicity (DLT) in these patients. A preliminary assessment of efficacy will also be made by enrolling an expanded cohort of patients at the MTD in the phase II portion of the study.

The study population is patients with relapsed or refractory T- or NK-cell lymphoma of with the following histologies: blastic NK-cell lymphoma, adult t-cell lymphoma/leukemia, t-cell prolymphocytic leukemia, t-lymphoblastic lymphoma, unspecified peripheral t-cell lymphoma, angioimmunoblastic t-cell lymphoma, anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, enteropathy-type t-cell lymphoma and hepatosplenic γ/δ t-cell lymphoma.

Patients eligible for treatment on this protocol will be treated with intravenous clofarabine for three consecutive days approximately every three weeks. For the phase I portion of the trial, an accelerated titration design will be utilized until certain toxicity criteria have been met. Then, a standard titration design will be used for the remainder of the phase I portion of the trial. Once the maximum tolerated dose has been defined, a Simon minimax two-stage design will initiate. To complete this study, we expect to enroll 20-38 patients over 18 months.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

- To determine the maximum tolerated dose of intravenous clofarabine using the schedule outlined below that can be administered safely to patients with relapsed and refractory T- and NK-cell lymphomas.
- To define the toxicity of clofarabine using the proposed schedule in patients with relapsed and refractory T- and NK-cell lymphomas.
- To make a preliminary assessment of efficacy of intravenous clofarabine at the maximum tolerated dose in patients with relapsed and refractory T- and NK-cell lymphomas.
    - The primary statistical endpoint to evaluate efficacy in the phase II portion will be response rate. Data will also be collected on response duration.

3.1 BACKGROUND AND RATIONALE

3.2 T-cell lymphomas-Classification

T- and NK-cell lymphomas form a heterogeneous group of Non-Hodgkin's lymphomas (NHLs). They are relatively uncommon, comprising 10-15% of all newly diagnosed NHL in the U.S. The proportions are reversed in Asia where 70-80% of NHL may be of the T-cell phenotype. Under the World Health Organization (WHO) classification schema, T-cell lymphomas are divided into disorders that are precursor T-cells, predominantly extranodal or predominantly nodal lymphomas. These categories are further subclassified into the following entities:

Precursor T-cell lymphoma/leukemia	**Predominantly Nodal**	**Predominantly Extranodal**
Blastic NK-cell lymphoma	**Peripheral T-cell Lymphoma, unspecified**	**Transformed Mycosis Fungoides**
NK/T-cell lymphoma/leukemia	**Angioimmunoblastic T-cell lymphoma**	**Subcutaneous panniculitis-like T-cell lymphoma**
Adult T-cell lymphoma/leukemia	**Anaplastic Large Cell lymphoma**	**NK/T-cell lymphoma, nasal type**
T-cell prolymphocytic leukemia		**Enteropathy-type T-cell lymphoma**
T-lymphoblastic lymphoma		**Hepatosplenic γ/δ T-cell lymphoma**
T-cell Large Granular Lymphocytic Leukemia		Lymphomatoid papulosis

Primary cutaneous anaplastic large cell lymphoma

Mycosis Fungoides/ Sezary Syndrome

Entities in bold type are eligible for this trial

3.3 T-cell Lymphomas: Prognosis

Most of the T- and NK-cell lymphomas are aggressive diseases requiring systemic chemotherapy and are associated with a poorer prognosis compared to their B-cell counterparts. Larger clinical series of T-cell lymphomas report median survivals of less than 2 years [1-3] and 5-year survival rates between 20-30% [1-4]. Failure-free survival for IPI intermediate and high risk patients is between 0-10% in the larger series with no plateau on the curves for these populations [2-4]. This poor prognosis is related to both decreased sensitivity to chemotherapy with lower response rates than their intermediate grade B-cell counterparts as well as a propensity for T-cell lymphomas to present with poor risk factors. In the series by Lopez-Guillermo, only 43% (62/144) of patients with non-anaplastic large cell T-cell lymphoma achieved a complete response (CR) while a nearly equivalent number, 41% (59/144) were non-responders to therapy [2]. Poor risk patients had similarly poor response rates in other studies with CR rates of 42% and 39% [4, 5].

3.4 Relapsed and Refractory T-cell Lymphomas: Therapy

There are few studies which specifically investigate optimal treatment regimens for patients with T-cell lymphomas. Instead, most patients with T- or NK-cell lymphomas have been treated like aggressive B-cell lymphomas. Based on a retrospective analysis of a series of T-cell patients, the prognosis for T-cell lymphomas is worse than B-cell lymphomas. This difference is primarily seen among the high and high-intermediate risk patients by International Prognostic Index (IPI). Five-year overall survival and disease-free survival were only 26% and 20%, respectively. Hence, many patients with T-cell lymphomas fail to achieve a complete response to initial therapy, and many others experience an early relapse [3, 6]. For example, 50% of patients with peripheral T-cell lymphoma present with stage IV disease which is associated with a 10% four-year disease-free survival [7]. Therefore, while T- and NK- lymphomas are not common, most patients will relapse and become refractory to therapy.

High dose therapy followed by an autologous transplant or less commonly an allogeneic stem cell transplant is a common treatment strategy for relapsed and refractory T-cell lymphomas. Transplantation has only been successful in patients with chemosensitive disease. For those patients who have chemosensitive disease and are transplanted, a

subset of patients will be cured. The remainder of these patients, who either are not chemosensitive at relapse or relapse after high dose therapy and stem cell transplantation, are left without curative treatment options. In order to improve the outcome in this patient population, novel agents need to be investigated to find an effective treatment regimen.

There have been relatively few studies exploring the utility of specific agents in relapsed T-cell lymphomas. Existing data is largely limited to small series, pilot studies, and retrospective experience. These results are described below.

For patients with relapsed and refractory T-cell lymphomas (T-cell NHL), deoxycoformycin (pentostatin) has been utilized with some success. It has been associated with a 50% overall response rate (ORR) and a 7% CR in relapsed patients with T-cell NHL (n=14). Despite its relatively high response rate in these heavily-pretreated patients, the median duration of response was only 6 months [8]. Another deoxycoformycin study conducted in relapsed/refractory mature T-cell malignancies showed an ORR of 38%. Greater than 50% of the responses were seen in patients with Sezary syndrome. Forty-eight percent of patients with T-cell prolymphocytic leukemia (T-PLL) responded to deoxycoformycin; three of whom had a CR lasting 8 -12 months [9]. Although single-agent deoxycoformycin may be active in many T-cell malignancies, the responses are not durable.

There are two series of patients with relapsed or refractory T-cell lymphoma treated with gemcitabine, a deoxycytidine analogue. In a small study of 10 patients who had 2 – 3 prior therapies for their T-cell lymphoma, 1200 mg/m2 of weekly gemcitabine resulted in a 60% ORR and a 20% CR, with a median duration of response of 13.5 months [10]. Forty-four patients with previously treated mycosis fungoides and peripheral T-cell lymphoma (PTCL) were enrolled in a larger phase II trial and treated with the same dose and schedule of gemcitabine. Seventy percent responded to therapy; 11% of whom achieved a CR. Treatment with gemcitabine was well-tolerated and resulted in a 15 month median duration of response in patients achieving a CR.

Alemtuzumab, a humanized anti-CD52 monoclonal antibody has been used in the treatment of relapsed or refractory T-cell lymphomas, particularly in T-PLL and PTCL. Keating, et al conducted a retrospective analysis of 76 patients with heavily pretreated T-PLL. These patients achieved a 51% ORR and a 39.5% CR. The median time to progression (TTP) was 4.5 months [11]. In a prospective phase II trial, patients with relapsed T-PLL who were treated with alemtuzumab achieved a 76% ORR and a 60% CR. The median disease-free interval was 7 months, a significant improvement from the brief response (3 months) associated with conventional CHOP therapy or pentostatin [12]. In another phase II trial, alemtuzumab was given to 14 patients with heavily-pretreated PTCL and found to have an ORR 36%. However, these positive results were mitigated by a high treatment-related mortality of 35% [13].

Denileukin diftitox, or ONTAK, a fusion protein composed of the receptor-binding domain of IL-2 and diphtheria toxin, is approved for cutaneous T-cell lymphoma.

Preliminary results from a phase II study of denileukin diftitox in relapsed/refractory B- and T-cell NHL demonstrated an ORR of 21% (n= 28). Responses were seen in both B- and T-cell lymphomas as well as CD25+ and CD25- tumors [14]. Other studies using denileukin diftitox as a single agent and in combination with CHOP for the treatment of PTCL are underway.

3.5 Rationale for use of clofarabine in relapsed and refractory T- and NK- cell lymphoma

T- and NK-cell lymphomas are rare malignancies and comprise a poor prognosis subset of NHL. With the exception of transplantation which cures only a minority of patients, there are no curative options for patients with relapsed T-cell malignancies. Many of these patients are refractory to standard chemotherapy and thus, they are not candidates for high dose therapy and stem cell transplantation. Even among the patients who received transplants, many will relapse and die of their disease. Due to the lack of effective treatments for the majority of those with T- and NK-cell lymphoma, active drugs are sought to ultimately improve the long-term outcome of these patients.

Nucleoside analogues are widely utilized and among the most active agents for the treatment of hematologic malignancies. The cytosine analogue, gemcitabine, is active against both Hodgkin's and Non-Hodgkin's lymphoma. As mentioned in section 3.3, this agent also has activity against relapsed and refractory T-cell lymphoma [10, 15]. A guanosine analog, nelzarabine or arabinosyl guanine prodrug, has activity against T-cell ALL and CLL [16]. The deoxyadenosine analogues, fludarabine, cladribine and deoxycoformycin, have varying degrees of activity against CLL, hairy cell leukemia, lymphoma and Waldenstrom's macroglobulinemia. In several studies, deoxycoformycin has produced responses in patients with T-cell malignancies. At Memorial Sloan-Kettering Cancer Center, the use of deoxycoformycin is also being explored as part of an upfront combination treatment regimen for patients with T-cell NHL.

Clofarabine, a second-generation deoxyadenosine analogue, was developed in order to increase efficacy and minimize toxicity compared to the first-generation agents such as fludarabine, cladribine, and deoxycoformycin. Like fludarabine and cladribine, it requires intracellular phosphorylation by deoxycitidine kinase to be metabolized to the cytotoxic triphosphate form. Fludarabine inhibits DNA synthesis through DNA polymerase; whereas, cladribine accomplishes this task through inhibition of ribonucleotide reductase. Clofarabine triphosphate inhibits both DNA polymerase and ribonucleotide reductase. In addition to its more potent inhibition of DNA synthesis, clofarabine is also an attractive agent to investigate based on promising results in early trials for both myeloid and lymphoid leukemias.

In a phase I trial conducted at the MD Anderson Cancer Center, a 16% overall response rate was observed in adult patients with relapsed acute leukemia who were treated with 5

days of clofarabine at doses between 11.25 and 55 mg/m^2/d. Six patients with either CLL or lymphoma were also treated on this protocol at lower doses. Two of the CLL patients had a partial response at the 15 mg/m^2/d dose [17]. In another phase I trial conducted in heavily pretreated pediatric patients with acute leukemia, a 32% overall response rate was observed; 20% of whom achieved a complete remission. Thirty-two percent of adult patients with relapsed or refractory acute myeloid leukemia achieved a complete response in a phase 2 trial conducted by Kantarjian, et al [18]. Additional trials with clofarabine are ongoing in patients with relapsed or refractory lymphoma and ALL.

To date, only two patients with T- or NK-cell lymphoma have been treated with clofarabine; both of whom achieved a complete response. In the 3 phase I/II trials mentioned above, there was one patient with a T-cell malignancy who was treated with clofarabine [19]. This patient achieved a complete remission after failing to respond to 3 prior regimens. To our knowledge, only one other patient with a T-cell malignancy has been treated with this agent. This patient had recurrent T-cell lymphoblastic lymphoma and achieved a complete remission after 2 cycles of clofarabine (52 mg/m^2/d for 5 days). He was treated on protocol at this institution and failed 3 prior salvage therapies. Further study of clofarabine is warranted given the limited treatment options for patients with T- or NK-cell lymphoma.

In the phase I trial of patients with both solid and hematologic malignancies, there were two dose-limiting toxicities [17]. In the patients with solid tumors including those with CLL and lymphoma, the dose-limiting toxicity was myelosuppression. For these patients, the maximum tolerated dose (MTD) was defined at 2 mg/m^2/d for 5 days. Myelosuppressive toxicity was graded differently for patients with acute leukemia. For these patients, failure of the leukocyte count to return to normal within 6 weeks of initiation of therapy was a dose-limiting toxicity. Since prolonged myelosuppression was not observed in the patients with acute leukemia, the dose of clofarabine was escalated to 55 mg/m^2/d for 5 consecutive days. Two of the 4 patients treated at 55 mg/m^2/d had a grade 3 hepatic toxicity. The maximum tolerated dose for this group of patients was 40 mg/m^2/d for 5 days.

The animal studies and early phase I/II trials of clofarabine have used the 5 consecutive day schedule based on prior experience utilizing this schedule in other nucleoside analogues such as fludarabine. The only alternative dosing schedule studied for clofarabine is once weekly. Results utilizing the once weekly dosing have not been reported to date. Plasma pharmacokinetic data performed in the phase II trial investigating the use of clofarabine in patients with relapsed leukemia demonstrated a higher plasma clofarabine triphosphate level at the end of infusion on day 3 compared to the levels at the end of days 1 and 2. More specifically, the level was 10 μM, 20 μM, and 25 μM at the end of the second, third and fourth infusion, respectively. In a second

patient, the clofarabine triphosphate concentration in the plasma increased more rapidly (30 μM at the end of the first infusion to 65 μM at the end of day 3) [17-19].

Due to the variability in the plasma clofarabine triphosphate levels and lack of rationale for a 5 consecutive day schedule, we are proposing an alternative schedule. Lymphomas are particularly sensitive to other purine analogues as evidenced by increased retention of plasma triphosphate concentrations. For example, the elimination half-life of fludarabine is much longer in patients with lymphoid malignancies compared to relapsed leukemia (24 hours vs. 7 hours). In the phase II clofarabine study, high levels of plasma triphosphate (40 μM) were required to achieve the maximum tolerated dose in relapsed leukemia. The triphosphate level within the blasts was less than 5 μM [18]. Since most of the patients treated on phase I trials have been relapsed leukemia patients, the pharmacodynamics for patients with lymphoid neoplasms in unknown. Because of increased lymphoid cell sensitivity to purine analogs and the possibility of longer elimination as well as our belief that single dosing is suboptimal, a 3 consecutive day schedule is being proposed for this study.

As clofarabine will be administered for 3 consecutive days instead of 5 days, the starting dose for the first cohort of patients was increased to 4 mg/m^2/d. This dose is similar to the MTD for solid tumor patients (12 mg/m^2/wk compared to 10 mg/m^2/wk for those who were treated at the MTD with the 5 day schedule). The DLT at this dose in the solid tumor study was myelosuppression. Since duration but not degree of myelosuppression is a defined DLT in this study and this dose was safe in other ways, we have chosen it as our starting dose and expect the MTD to occur at a higher dose level than observed in patients with solid malignancies but lower than that of the leukemia patients (200 mg/m^2/wk). [17].

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single institution, open-label, phase I/II study designed to evaluate the safety and efficacy of intravenous clofarabine in patients with previously treated T- and NK-cell lymphomas. During the phase I portion of the study, cohorts of patients will be treated with escalating dose levels of clofarabine. Once the maximum tolerated dose has been defined, additional patients will be accrued to the phase II portion of the study.

4.3 Intervention

Patients will receive intravenous clofarabine once daily for three consecutive days. Doses of clofarabine will start at 4 mg/m^2/day and will be escalated to higher dose levels as described in Section 9.2. If the toxicity criteria have not been exceeded at the day 22 ±

2 evaluation, the next course of therapy will be administered. Interim restaging, as defined in Section 9.6, will be performed at the conclusion of 2 cycles of clofarabine. The dose-limiting toxicities will be based on the **first** cycle of therapy.

4.4 Duration of therapy

Treatment may continue as long as there is a clinical benefit as defined below and the criteria for removal from study has not been met as defined in Section 13.0. After 2 cycles of clofarabine, patients will be permitted to receive additional cycles if they have either stable disease or a response (PR or CR). (Refer to Section 12.2 for definitions of response.) After 4 cycles of treatment, only those patients who achieved either a PR or CR may receive additional cycles of the study drug. Responding patients can be treated up to 2 cycles beyond their maximum response.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 Clofarabine

Clofarabine ([2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) adenine]; Cl-F-ara-A; CAFdA) is a second-generation purine nucleoside analogue which was designed as a hybrid molecule of fludarabine (F-ara-A) and cladribine (2-CdA, CdA). Because clofarabine has a chloro group at the 2-position of adenine, its chemical structure is more closely related to CdA than to F-ara-A. Halogenation at the 2-position of adenine renders this class of compounds resistant to cellular degradation by the enzyme adenine deaminase [20].

Clofarabine is a white to off white solid. It is formulated at a concentration of 1 mg/mL in sodium chloride (9 mg/mL) and water for injection. An investigational supply of clofarabine will be supplied by Genzyme in 2 vial sizes: a 10 mL flint vial and a 20 mL flint vial. Then 10 mL flint vial contains 5 mL (5mg) of solution and the 20 mL flint vial contains 20 mL (20 mg) of solution. Vials should be stored at room temperature (15-30^{o}C). Clofarabine is stable for 24 months at 25^{o}C and 60% relative humidity and for 6 months at 40^{o}C and 75% relative humidity. Clofarabine for injection should be filtered through a sterile 0.2 μm syringe filter and then further diluted with 5% dextrose injection (D5W) USP or 0.9% sodium chloride injection USP. The resulting admixture can be stored at room temperature but should be used within 24 hours. (See Investigator's Brochure)

Clofarabine is sequentially metabolized intracellularly by deoxycytidine kinase to the active 5'-triphosphate metabolite. It has a high affinity for the activating phosphorylating enzyme, deoxycytidine kinase, equal to or greater than that of the natural substrate, deoxycytidine. Clofarabine inhibits DNA synthesis by decreasing cellular deoxynucleotide triphosphate pools through an inhibitory action on ribonucleotide reductase, and by terminating DNA chain elongation by competitive inhibition of DNA polymerases. The affinity of clofarabine

triphosphate for these enzymes is similar to or greater than that of deoxyadenosine triphosphate. In preclinical models, clofarabine has demonstrated the ability to inhibit DNA repair by incorporation into the DNA chain during the repair process. Clofarabine 5'-triphosphate also disrupts the integrity of mitochondrial membrane, leading to the release of the pro-apoptotic mitochondrial proteins, cytochrome C and apoptosis-inducing factor, leading to programmed cell death [21-25].

Clofarabine has been shown to be active against a wide range of in vivo and in vitro human tumor models, including solid and hematologic tumor types [26]. Toxicology studies of clofarabine in mice, rats, and dogs showed that rapidly proliferating tissues were the primary target organs of toxicity, and except for the cardiotoxicity and hepatotoxicity seen in rats treated with clofarabine, these results were similar to those observed in studies with cladribine and fludarabine [26] Additionally, the developmental toxicities, including growth retardation and skeletal alterations, observed in rats and rabbits are characteristic effects of chemotherapeutic agents like cyclophosphamide that are capable of altering the normal pattern of apoptosis and/or altering DNA function [26].

To date, there are three published trials investigating clofarabine in acute leukemia, solid tumors and lymphoproliferative disorders [17-19]. The MTD of clofarabine in adult patients has been determined to be 40 mg/m^2/day in acute leukemia, which is slightly lower than the tolerable daily dose for pediatric patients, 52 mg/m^2/d. Patients with acute leukemia who were treated with higher doses of clofarabine in the two phase I and one phase II trials experienced grade 3 fatigue, hypotension, hyperbilirubinemia, transaminitis, nausea/vomiting, diarrhea, rash and/or palmoplantar erythrodysesthesia. The only grade 4 toxicity was hepatic which occurred at 40 mg/m^2/d in 3 adults and 70 mg/m^2/d in 1 child. Other grade 1 or 2 toxicities include myalgias, arthralgias, anorexia, constipation, mucositis, edema, drug fever and neurologic toxicity. For the patients with either a solid tumor or lymphoproliferative malignancy, the dose-limiting toxicity was myelosuppression. This was not a toxicity for the leukemia patients since myelosuppressive toxicity, for this patient group, was defined as marrow with less than 5% cellularity and without evidence of leukemia, lasting more than 6 weeks from the start of therapy. The non-hematologic toxicities for the patients with solid tumors or lymphoproliferative disorders occurred infrequently and were mild. Grade 1 nausea and anorexia were noted in two out of 19 treated patients [17]. Overall, the treatment was very well-tolerated.

As of 01 October 2004, a total of 377 patients (245 adult patients and 132 pediatric patients) have been treated with clofarabine in 4 phase I trials, 6 phase II trials, and an emergency expanded access program [27]. In patients who were treated at dose levels which varied from 2 mg/m2/d up to 70 mg/m2/d, the most common toxicity which occurred in 25% (94/377) of patients was a grade 3 or 4 infection. The majority of these infections were of bacterial origin. A few of these events were attributed to fungus (n=5) or were of a viral origin (n=6). Greater than 5% of patients but less than 10% had a Grade 3/4 fever and/or

fever/neutropenia. Except for infection, fever, and fever/neutropenia, there were no other non-hematologic toxicities which occurred in at least 5% of patients.

A decrease in left ventricular systolic function of unclear etiology has been observed in pediatric acute leukemia patients (n=55) treated with clofarabine at the 52 mg/m^2/d dose level. In the phase II study (unpublished data)[28], the change in systolic function was transient in the majority of cases. On close inspection, the timing of the decrease in systolic function coincided with other clinical events such as sepsis and may have been related to either the clinical event itself or the drug(s) used to treat the problem. Unfortunately, in some cases, the decrease of LV function occurred when clofarabine was given within 6 months of the last anthracycline dose, making it impossible to determine if the decline was related to clofarabine or to the prior anthracycline therapy. Of note, clofarabine was given to one child with preexisting severe LV dysfunction with no significant further deterioration.

Small pericardial effusions were a frequent finding. They did not result in any significant hemodynamic effect and required no intervention. They were detected more frequently in the initial patients entered on the trial and the effusions were almost absent in the later patients. This may reflect changes in the protocol made to accommodate the fluid retention seen in the early patients [28].

Capillary leak syndrome also occurred rarely in 4 out of 60 pediatric leukemia patients [28]. Again, all of the pediatric patients were treated at the 52 mg/m^2/d dose. There were 2 patients who had grade 4 capillary leak syndrome which resulted in death and may have been from the study drug. There was one patient had a grade 3 adverse event. Concurrent medical conditions such as sepsis and/or disease progression may have made these patients susceptible to this toxicity.

In this study, the starting dose of 4 mg/m^2/d for 3 consecutive days was chosen based on the MTD for both solid and lymphoproliferative disorders. In all of the published clofarabine trials, patients were treated for 5 consecutive days. With a MTD of 2 mg/m^2/d, patients with solid and lymphoproliferative disorders received a weekly total dose of 10 mg/m^2/wk. With a starting dose of 4 mg/m^2/d for 3 consecutive days, patients will receive 12 mg/m^2/wk. We predict that the DLT will occur around the third dose level since it is defined differently compared to the prior trials. The DLT, in this study, is defined in terms of delayed count recovery rather than grade 3 or 4 myelosuppression at any time following treatment.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Patients must have a diagnosis of T- or NK-cell NHL with one of the following subtypes: Blastic NK cell lymphoma; NK/T-cell lymphoma/leukemia; Adult T-cell lymphoma/leukemia; T-cell PLL; T-lymphoblastic lymphoma; Peripheral T-cell lymphoma, not otherwise specified; Angioimmunoblastic T-cell lymphoma; Anaplastic large cell lymphoma; transformed mycosis fungoides; Subcutaneous panniculitis-like T-cell lymphoma; Nasal T/NK cell lymphoma; Enteropathy-type T-cell lymphoma; Hepatosplenic γ/δ T-cell lymphoma.
- Patients must have been previously treated with cytotoxic chemotherapy and/or monoclonal antibody and be without a standard curative treatment option. For the purposes of this trial, allogeneic bone marrow transplantation is not considered a standard curative option.
- Patients must be off any other therapy such as interferon, antibody therapy, retinoids, or other non-chemotherapeutic treatments for $\geq$ 3 weeks prior to beginning treatment on study. Stable doses of corticosteroids will be allowed.
- Patient must be off any conventional chemotherapy or radiation therapy (encompassing a substantial [>10%] amount of bone marrow) within 4 weeks (6 weeks for nitrosoureas ormitomycin C) prior to study.
- Good performance status (ECOG 0 – 2)
- Age $\geq$ 2 years.
- Patients must have adequate organ and marrow function as defined below:

Phase I eligibility criteria

○ absolute neutrophil count	$\geq$ 1,500/uL
○ platelets	$\geq$ 100,000/uL
○ serum creatinine	$\leq$ 1.0 mg/dL or estimated GFR > 60 ML/min
○ total bilirubin	$\leq$ 2.0 X normal institutional limits
○ AST (SGOT)/ALT (SGPT)	$\leq$ 2.5 X institutional upper limit of normal

Phase II eligibility criteria

○ absolute neutrophil count	$\geq$ 500/uL
○ platelets	$\geq$ 50,000/uL
○ serum creatinine	< 2.0 mg/dL*
○ total bilirubin	$\leq$ 2.0 X normal institutional limits*
○ AST (SGOT)/ALT (SGPT)	$\leq$ 2.5 X institutional upper limit of normal*

*For the phase II portion of the study, the investigator may make an exception if the laboratory abnormality is due to lymphoma.

- For the phase I portion of the trial, patients must have **evaluable** disease.
- For the phase II portion of the trial, patients must have measurable disease defined as any nodal site or mass lesion ≥ 1.5 cm in longest transverse diameter on physical exam or computed tomography scan or a measurable extranodal site > 1 cm.
- For patients with primarily blood or marrow based disease, evaluable patients will be eligible
- Signed informed consent and/or assent.

6.3 Subject Exclusion Criteria

- Active infections requiring antibiotics.
- Pregnant or lactating women. (Women and men of childbearing age should use effective contraception).
- New York Heart Association class III/IV congestive heart failure
- Patients seropositive for infection with Human Immunodeficiency virus (HIV-1) are excluded from the study because of the potential for serious infectious complications associated with a T-cell suppressive therapy in these patients.
- Concurrent active malignancy requiring therapy (other than a synchronous T/NK-cell NHL).
- Receipt of systemic corticosteroids within 7 days of study treatment, unless patient has been taking a continuous dose of no more than 10mg/day of prednisone for at least 1 month.
- Other serious or life-threatening condition(s) deemed unacceptable by the principal investigator.

Please note copies of source documentation confirming eligibility for patients enrolling at outside institutions must be provided to the MSKCC CTO registrar at the time of registration. Please fax to 212-557-0786 and PPR 646-735-0008/0003.

7.0 RECRUITMENT PLAN

Recruitment Plan

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC-Lead Center), University of Rochester Medical Center, and The Cleveland Clinic. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

8.1 PRETREATMENT EVALUATION

The following tests are required prior to beginning therapy:

Within 2 weeks prior to starting on protocol:

- Relevant history and physical exam.
- The following blood tests will be required: CBC with differential, comprehensive profile, phosphorous, uric acid, LDH, PT and PTT**.**
- Urinalysis
- Urine or serum pregnancy test for woman with childbearing potential.

Within 1 month prior to starting on protocol:

- Bone marrow biopsy for histology and immunohistochemistry.
- Chest X-ray
- EKG
- Echocardiogram or MUGA
- CT scan of the chest, abdomen and pelvis.
- CT scan or MRI of relevant extranodal sites not included in chest, abdomen, and pelvis. (e.g. nasopharynx)
- PET scan (not required but encouraged)
- HIV test
- Hepatitis B surface antigen and antibody
- Hepatitis C antibody

- HTLV-1 antibody

9.1 TREATMENT/INTERVENTION PLAN

9.2 Pre-treatment Procedures

- Pretreatment laboratory evaluation: CBC with differential, Cr, AST, ALT, Alk Phos, Bili
- Premedication: Standard anti-emetics for a moderately emetogenic medication will be given. Hydrocortisone 100 mg/m2 will be administered 30 minutes prior to each dose of clofarabine on cycles 1 and 2.
- Prehydration: 500 mL NS IV over 30-60 minutes.

9.3 Clofarabine

Clofarabine will be infused intravenously over 1 hour and will be administered daily for 3 consecutive days. In the phase I portion of this study, the dose levels will be determined by the dose escalation schema in Table 9.0. Cycles will be repeated as early as day 22 ± 2 days or up to 2 weeks later (or 36 ± 2 days) if the patient meets retreatment criteria as defined in section 9.4.

Table 9.0 Dose Escalation Schema

Dose Level	Dose (mg/m^2/day)	% Increase	Multiple of Initial Dose
1	4	-	-
2	8	100	2.0 n
3	13.2	67	3.3 n
4	20	50	5.0 n
5	28	40	7.0 n
6	36	33	9.0 n
7	49	28	12.3 n

Refer to Section 14.1 for more details regarding dose escalation. Once the MTD of clofarabine has been identified, the remainder of the patients will be accrued to the phase II portion of the study.

9.4 Supportive Medication (standard)

- **Sulfamethoxazole-trimethoprim DS bid will be administered for three consecutive days each week (typically Monday, Tuesday, and Wednesday)** as pneumocystis carinii pneumonia (PCP) prophylaxis. Patients who are allergic to sulfa may receive alternate prophylaxis such as aerosolized pentamidine 300 mg once per month. PCP prophylaxis will begin with the first cycle of chemotherapy.
- **Acyclovir 400 mg po bid or the renally adjusted equivalent will be administered as prophylaxis against Herpes Zoster.** It will begin with the first cycle of chemotherapy.
- Darbepoietin or erythropoietin may be administered as per hospital policy. Discontinuation of either of these medications or increasing the dose is based on standard dose and response criteria.
- Growth colony stimulation factor should be administered beginning 24-72 hours after the conclusion of each 3 day treatment cycle. The type and dose of the growth colony stimulation factor will be determined as per hospital policy.

9.5 Re-treatment criteria

Patients will receive additional cycles of clofarabine as long as they meet the following criteria **at the time of re-treatment**:

- ANC $\geq$ 1000 cell/µl (or ANC $\geq$ 500/µl for patients who were enrolled at this level in the phase II portion of the trial only)
- Platelet $\geq$ 75,000 /µl (or platelet $\geq$ 50,000/µl for patients who were enrolled at this level in the phase II portion of the trial only)
- Non-hematologic toxicity: if the toxicity is less severe than a grade 4 infection and/or a grade 4 hemorrhage, and it resolves to $\leq$ grade 1 or baseline as per CTCAE v3.0 toxicity criteria at the time of retreatment.

Repeat cycles of clofarabine are administered on approximately a 21 day schedule unless the patient does not meet re-treatment criteria as defined above. For those patients who do not meet the above parameters at the day 22 $\pm$ 2 evaluation, their next cycle of therapy may be held up to 2 weeks. After any treatment delay, the patient will be re-evaluated the following week (up to day 36 $\pm$ 2 days). If the patient meets re-treatment criteria at the next evaluation, the next cycle of clofarabine will be administered at the full dose. If the patient does not meet re-treatment criteria at both the day 29 $\pm$ 2 and the day 36 $\pm$ 2 evaluation, this patient will be **removed** from the study **unless there has been a prior documented response (CR or PR) to therapy**.

In these cases, patients must meet all of the criteria defined in section 9.8. The dose of clofarabine will then be adjusted accordingly.

9.6 Interim Laboratory Evaluation

- weekly cbc with differential in the first cycle; then evaluation every 1 - 2 weeks, as indicated
- weekly comprehensive profile in the first cycle; then evaluation every 1 - 2 weeks, as indicated

9.7 Restaging

9.6.1 Following each course of clofarabine (every 2 cycles)

- CT scan of chest/abdomen/pelvis
- CT scan or MRI of relevant extranodal sites not included in the CT of the chest/abdomen/pelvis
- PET scan encouraged if previously positive

9.6.2 End of study

- CT scan of chest/abdomen/pelvis
- CT scan or MRI of relevant extranodal sites not included in the CT of the chest/abdomen/pelvis
- PET scan encouraged if previously positive
- Bone Marrow biopsy (if previously positive and if patient is in CR by other criteria)
- Echocardiogram if the dose of the clofarabine is ≥ 28 mg/m^2/day

9.7 Treatment beyond 2 cycles

9.7.1 Following 2 cycles of clofarabine

Patients with stable disease, a partial response, or a complete response will receive 2 more cycles of clofarabine.

9.7.2 Following 4 cycles of clofarabine

Patients with a partial response or a complete response will receive 2 more cycles of clofarabine. Patients may be treated up to 2 cycles beyond their maximum response.

9.7.3 Progression of disease

Patients with progression of disease at any time will be declared treatment failures and removed from the study.

9.8 Dose reduction

Patients can be retreated with clofarabine at a reduced dose if all the following conditions are met:

- Clinical or radiologic response (PR or CR)
- The non-hematologic toxicities in the prior cycle were not a life-threatening infection or hemorrhage
- Re-treatment criteria have been met as defined in section 9.4

Determination of Dose
If the above conditions are met, patients will be treated at the next lower dose level.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Prior to each cycle of chemotherapy, the patient will have an interval history, toxicity evaluation and physical examination, including vital signs, and performance status.

10.2 CBC with differential, and comprehensive profile will be required prior to each cycle of chemotherapy.

10.3 After completion of 2 cycles of clofarabine, the patient will be assessed or reassessed for response as per section 9.6.

10.4 If the patient has achieved a complete response (CR), a repeat bone marrow biopsy will be performed only in those cases where it had been previously positive.

10.5 Following completion of the treatment plan, responding patients should be followed at three month intervals for the first two years post-therapy to document duration of response.

Table 10.0 Study Calendar

Assessments	Pre-treatment ≤ 30 days prior to Rx	Pre-treatment ≤ 14 days prior to Rx	Day 1 Cycle 1	Day 8 Cycle 1	Day 15 Cycle 1	Day 22, 29, 36 Cycle 1[a]	Day 1 Cycle 2	Day 8 Cycle 2	Day 15 Cycle 2	Day 22, 29, 36 Cycle 2[a]	Off study/ Cont Rx
Clofarabine			XXX				XXX				
Informed consent and/or assent		X									
Medical history and height (cm)		X									
Interval history, incl. AE eval. and med list		X	X			X	X			X	X
PE, VS, incl.. wt and ECOG PS		X	X			X	X			X	X
Cbc with differential		X	X	X	X	X	X		X	X	X
Serum chemistry[b]		X	X	X	X	X	X		X	X	X
LDH		X									X
Coagulation profile / urinalysis		X									
Beta-HCG[c]		X									
Viral serologies[d]	X										
EKG	X										X
Echo or MUGA	X										X[e]
Chest Xray	X										
Tumor imaging[f]	X										X
Bone marrow biopsy	X										X[g]

[a]If the re-treatment criteria is not met at the day 22 ± 2 day evaluation, the treatment will be withheld and the patient will be re-evaulated the following week(s),up day 36 ± 2 days from the beginning of therapy.
[b]Serum chemistry: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT (AST), SGPT (ALT), sodium, magnesium, uric acid
[c]Serum or urine beta-HCG is required for all women of childbearing potential.
[d]Viral serologies: HIV, Hep B S Ag, Hep B S Ab, Hep C Ab, HTLV-1
[e]Echocardiogram/MUGA: A followup echocardiogram or MUGA must be ordered if the dose level is at or above 28 mg/m^2/d
[f]Tumor imaging: CT of the chest, abdomen and pelvis, and CT or MRI of extranodal sites (if indicated). Followup PET scan is encouraged (not required) only if baseline PET scan was positive
[g]Followup bone marrow biopsy is required only if: 1) previously positive and 2) disease is in complete remission per define criteria.

11.1 TOXICITIES/SIDE EFFECTS

As stated in section 5.0, the dose-limiting toxicity for patients with solid tumors or lymphoid malignancies was myelosuppression. For the patients with acute leukemia who were treated with much higher doses of clofarabine (40-52 mg/m^2/d), the dose-limiting toxicity was hepatotoxicity and rash. More specifically, potential toxicities include hyperbilirubinemia, transaminitis, neutropenia, leukopenia, thrombocytopenia, anemia, nausea, and vomiting. Other side effects which have been seen rarely in early trials include rash, myalgia, fatigue, diarrhea, constipation, mucositis, urinary incontinence, headache, fever, chills, anorexia, palmar-plantar erythrodysesthesia, anxiety, bone pain, cough, tachycardia, congestive heart failure, abdominal pain, seizure, hypertension, respiratory distress, and capillary leak syndrome.

An objective of this study is to obtain information on the safety and efficacy of clofarabine for patients with previously treated mature T-and NK-cell lymphoma. It is the Investigator's obligation to report all adverse experiences (AE's), regardless of association with study drugs.

11.2 Definitions of AE's

11.2.1 Adverse Experience: An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product which does not necessarily have a causal relationship or association with the treatment. Laboratory abnormalities should only be recorded as AE's if they are associated with clinical sequelae and/or require an intervention.

11.2.2 Serious Adverse Experience (SAE): An SAE is considered to be any experience occurring at any dose that results in any of the following outcomes: (1) is fatal or life-threatening ("Life-threatening" means that the event, as it actually happened, placed the subject at immediate risk of death.), (2) is disabling, (3) results in hospitalization or prolongation of hospitalization, or (4) results in congential anomaly or occurrence of malignancy. Important medical events that may not result in death may be considered SAE's when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.2.3 Expected Adverse Experience: Any AE that is identified in the current Investigator's Brochure or in Section 5 and/or Section 11 is considered an expected AE.

11.2.4 Unexpected Adverse Experience: An AE which is not previously reported (in nature, severity, or incidence) in the current Investigator's Brochure or general investigational plan.

11.3 Serious Adverse Experience Reporting Requirements

For Participating Sites:

Any SAE will be reported to the local institution's IRB. In addition, it will need to be sent to MSKCC as the coordinating center and Genzyme as soon as possible but no later than 5 days from the onset of the event.

The Study PI will fax a copy of all SAE's within 5 days to outside site principal investigators to report to their own local IRB's.

Participating sites should send the following information to the coordinating center:

1. The initials of the subjects, patient MRN #, MSKCC protocol # and title
2. The date the event occurred
3. A description of the SAE
4. An explanation of how the SAE was handled
5. A description of the subject's condition
6. Indication if the subject remains on the study
7. Indication if the event is considered related to the treatment (drug, device,intervention)
8. Indication if an amendment will need to be made to the protocol and/or consent form as a result of the SAE.
9. Name of the site and person reporting the event

Refer to section 17.2.

11.4 SAE Followup

For all SAEs occurring during the study, within 30 days of the last administration of study drug, or prior to alternative therapy (whichever occurs first), the investigator must submit follow-up reports to Genzyme regarding the patient's subsequent course until the SAE has subsided, or until the condition stabilizes (in the case of persistent impairment), the patient receives alternative treatment, or the patient dies.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response and progression of disease will be evaluated in this study using a modification of the international criteria proposed by the Cheson et al. [29].

12.1.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥15 mm with conventional techniques (PET, CT, MRI, x-ray). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

12.1.2 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 15 mm with conventional), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphoma cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

12.2 Response Criteria

Response criteria will be based on assessment following every 2 cycles of clofarabine. The criteria are as follows (GTD = Greatest Transverse Diameter; SPD = Sum of the Products of the Greatest Diameter):

12.2.1 Complete Remission (CR):

- No clinical, radiographic or diagnostic evidence of disease.
- No disease related symptoms.
- Abnormal biochemical values (eg. LDH) clearly attributable to lymphoma must have normalized.
- Lymph nodes, nodal masses regressed to "normal" size:
- If >1.5 cm before treatment, regressed to ≤ 1.5 cm in GTD.
- If 1.1 to 1.5 cm before treatment, regressed to ≤ 1 cm in GTD (or >75% in SPD).
- Spleen and all previously enlarged organs decreased in size. Spleen must not be palpable on exam
- Bone marrow free of disease on repeat aspirate and biopsy if initially positive.
- Normalization of PET scans.

12.2.2 Complete Remission/unconfirmed (CRU):

Patients meeting the above criteria for CR with the following exceptions:

- Residual node mass of >1.5 cm in GTD regressed by > 75% in SPD
- Individual nodes previously confluent regressed by >75% in SPD
- Indeterminate bone marrow (increased number or size of lymphoid aggregates without cytologic or architectural atypia.)

12.2.3 Partial Remission (PR)

- ≥ 50% decrease in SPD of the six largest dominant nodes/nodal masses.
- No increase in size of other nodes, liver or spleen.

- Splenic and hepatic nodes regressed at least 50% in SPD
- No new sites of disease.
- Bone marrow and organs other than the spleen and liver cannot be considered for evaluation for PR because involvement at these sites is considered evaluable but not measurable.

12.2.4 PET negative Partial Remission (PET- PR)

- Patient meets above criteria for PR with resolution of previous PET positive lesions.

12.2.4 Stable Disease (SD)

- Patients who have achieved less than a partial remission but who have not developed findings consistent with progressive disease.

12.2.5 Progressive Disease (PD)

- In patients previously CR, Cru, PR or SD.
- ≥ 50% increase in SPD of any previously identified abnormal node.
- Appearance of any new lesion during or at the end of therapy

13.0 CRITERIA FOR REMOVAL FROM STUDY

- Ineligibility of the patient as defined in inclusion/exclusion criteria
- Significant protocol violation
- Non-compliance of the patient
- Unacceptable toxicity which in the judgment of the investigator and/or treating physician renders further treatment on protocol contrary to the patient's best medical interest.
- Refusal of the patient to continue treatment and/or observation
- Unrelated medical illness or complication that increases the risk of protocol therapy to unacceptable levels.
- Progression of disease
- Decision by the Investigator that termination is in the patient's best medical interest.
- Loss to follow-up
- Death of the patient

14.1 BIOSTATISTICS

14.2 Study Endpoints

The two major objectives of this study are: (1) to determine the maximum tolerated dose of intravenous clofarabine using the schedule outlined above in patients with relapsed T- and NK-cell lymphomas and (2) to determine the response rate at this defined dose.

14.3 Study Design

To accomplish the first objective, an accelerated titration design will be used for the first patient. The next patient can be treated at the next dose level using the accelerated titration design if the currently treated patient does not had the following: 1) a grade 2 non-hematologic toxicity, or 2) a delay in the recovery of platelets or neutrophils at the day 22 ± 2 day evaluation.

If either of these criteria has been met (listed above), a standard titration scheme will be used where groups of at least three patients will be treated with escalating doses of clofarabine. A modified Fibonacci design was used to determine the size of the dose escalations.

Regardless of whether an accelerated or standard titration design is used, a patient cannot be enrolled to the next dose level (next cohort) until all patients within the current cohort satisfy one of the following: 1) the patient is off study, or 2) the patient has started the next cycle of clofarabine.

14.4 Dose-Escalation of clofarabine

Patients will be entered on the study and treated with clofarabine at an escalating dose as defined in section 9.2. Dose escalation will proceed as follows:

14.4.1 Accelerated titration design

- The next patient will be treated at the next dose level, if the patient does not have either: 1) a grade 2 non-hematologic toxicity, or 2) a delay in the recovery of platelets or neutrophils at the day 22 ± 2 day evaluation.

If the above criteria have not been met, the next patient will be enrolled at the **same** dose level using the standard titration design. See section 14.3.2.

14.4.2 Standard titration design

Refer to section 14.4 for the definition of DLT and MTD.

- If none of the initial three patients in a cohort experience dose-limiting toxicity (DLT), then a new cohort of three patients will be treated at the next higher dose level.

- If one of the three patients in a cohort experiences DLT, then up to three additional patients will be treated at the same dose level. Escalation will continue if only one of the six patients experiences DLT.

- If two or more patients in a cohort experience DLT, then the maximum tolerated dose (MTD) will have been exceeded, and no further dose escalations will occur. The previous dose level will be considered the MTD.

- If only three patients were treated at a dose level under consideration as the MTD, then up to three additional patients will be accrued. If no more than one of the six patients at that dose level experience DLT, then that dose level will be confirmed as the MTD. If two or more patients in that cohort experience DLT, then the previous dose level will be studied in the same fashion.

Accelerated Titration	
Number of Subjects with Drug Related DLT (Grade 2 non-hematologic toxicity or delay in platelet or neutrophil recovery at day 22) at a Given Dose Level	**Dose Escalation Rules**
0 of 1	Next patient can be treated at the next higher dose level
1 of 1	Convert to standard titration with this dose level and enroll 2 more subjects at this dose level
Standard Titration	
Number of Subjects with Drug Related DLT (as Defined in Section 14.4) at a	**Dose Escalation Rules**

Given Dose Level	
0 of 3	Next cohort of 3 subjects treated at the next higher dose level
1 of 3	3 more subjects are treated at that same dose level
≥2 of 3	Dose escalation stops and dose level is considered the Maximum Administered Dose (MAD). 3 more subjects will be added to the next lower dose level, unless 6 subjects have already been treated at that dose level
1 of 6	Next cohort of 3 subjects treated at the next higher dose level
> 2 of 6	Dose escalation stops and dose level is considered the Maximum Administered Dose (MAD). 3 more subjects will be added to the next lower dose level, unless 6 subjects have already been treated at that dose level
≤1 of 6 at the highest dose level below MAD	Maximum Tolerated Dose

Table V provides the probabilities of dose escalation based on true risk of toxicity for the standard phase dose escalation scheme.

Table V. Probability of Dose Escalation.

Risk of Toxicity	Probability of Escalation
0.10	0.91
0.20	0.71
0.30	0.49
0.40	0.31
0.50	0.17
0.60	0.08

14.4.3 Observation period

Regardless of whether an accelerated or standard titration design is used in the phase I portion of the trial, a patient cannot be enrolled to the next dose level (next dose level) until all patients within the current cohort satisfy one of the following: 1) the patient(s) are off study, or 2) the patient(s) have started the next cycle of clofarabine.

14.5 Definitions of DLT and MTD

DLT is defined as any of the following:

- **≥ Grade 2 thrombocytopenia (platelet < 75,000) lasting ≥ 36 ± 2 days from first day of clofarabine infusion,**
- **≥ Grade 3 non-hematologic toxicity according to NCI's CTCAE v 3.0**

MTD is defined as the highest dose studied for which the incidence of DLT is less than 33%. The percentage of patients who experience toxicity at each dose level will be calculated, with a 95% confidence interval.

14.6 Efficacy of single-agent clofarabine

The purpose of the phase II portion of the trial is to estimate the response rate for single-agent clofarabine using the maximum tolerated dose with the schedule outlined above. A Simon minimax two-stage design will be used in which a 10% response rate is considered not promising, a 35% is considered promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are both set at 0.10. In this scenario, the maximum number of patients accrued to the phase II portion of the trial would be 18 patients. In the first stage of the design, 8 patients will be accrued, i.e., an additional 2 patients to those who were treated at the MTD in the phase I portion. If one or more responses (either a PR or CR) are observed among these 8 patients, then an additional 10 patients will be accrued to the second stage. If there are no responses (PR or CR) among the initial 8 patients, the trial will be discontinued.

Using the minimax design, there is a 43% probability of stopping the trial early due to a non-promising therapy, or less than a 10% response rate. The drug is worthy of further investigation if there are 4 or more responses (PR or CR) of the 18 patients treated at the MTD. The design yields at least a 90% probability of a true positive result if the response rate (CR or PR) is at least 35%.

14.7 Toxicity and Response

Frequencies of toxicities based on NCI CTCAE, v 3.0 and response (using the criteria in Section 12.0) will be tabulated.

14.8 Patient Accrual and Duration of Study

A minimum number of three patients and a maximum number of 48 patients will be needed to complete this study if we assume that there are no more than 5 dose levels using the standard titration design. The Lymphoma Service will see approximately 1-2 patients each month who meet eligibility requirements for this trial. The amount of time required to complete this trial will depend on the number of dose levels studied, the number of patients accrued to each dose level, and the number of responses seen in the first stage of the phase II portion of the study. We anticipate that this trial will take approximately 1.5 years to complete.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration (at Memorial Sloan Kettering Cancer Center)

The following person(s) can obtain informed consent at MSKCC:

STEVEN HORWITZ, M.D
ANDREW ZELENETZ, M.D. Ph.D
TANYA TRIPPETT, M.D.
PAUL HAMLIN M.D.
MATT MATASAR, MD

Confirm with electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-

0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR.

For Participating Centers:

The following person(s) can obtain informed consent:

DEBORAH MULFORD, M.D., University of Rochester Medical Center
BRAD POHLMAN, M.D., The Cleveland Clinic

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center. To complete registration and enroll a patient from an outside center, the study coordinator will fax to Clinical Trials Office at MSKCC the completed MSKCC eligibility checklist, the last page of the signed informed consent, the signature page of the Research Authorization, and supporting source documentation for eligibility questions. If the patient meets all criteria, the patient will be enrolled and then the patient will be assigned a MSKCC study number. The MSKCC registrar will fax back an enrollment confirmation. Patients from all sites must be registered with the Protocol Patient Registration (PPR) at MSKCC before starting therapy, Telephone 646-735-8000, Fax 646-735-0008/0003, Hours of operation 8:30 am to 5:30 pm (Eastern Time) Monday through Friday.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]
Research Authorization	[Date]
MSKCC IRB Protocol#	
Attending of Record (if applicable)	[Last, First Name]
Consenting Professional	[Last, First Name]
Informed Consent Date	
Patient's Full Name	[Last, First Name]
Patient MRN	

15.3 Protocol Patient Number
Once eligibility has been established, the patient is assigned an MSKCC Clinical Research Database (CRDB) patient number. This number is unique to the patient and must be written on all data and correspondence for the patient.

15.4 Randomization

There is no randomization in this study.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secured database (Clinical Research Database, CRDB) at Memorial Sloan-Kettering Cancer Center.

Standardized Case Report Forms (CRFs) have been generated for this study. Affiliate sites will be responsible for filling out these MSKCC case report forms. Blank case report forms will be sent to the data managers at each site (for photocopying and use). These forms and the required source documentation must be submitted to MSKCC in a timely fashion (please see Appendix 1 for schedule of data collection forms). When a patient goes off-study all CRFs are required to be sent to MSKCC no later than 4 weeks after the off-study date. Participating sites must fax case report forms (212) 557-0787 to the attention of the RSA.

Forms can also be mailed or emailed to the address below.
Memorial Sloan-Kettering Cancer Center
Clinical Trials Office
Hanna Weissbrot
633 Third Avenue – 15th floor
New York, NY 10017
weissbrh@mskcc.org

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extext and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation

17.1 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research

Clofarabine is approved for the trearment of pediatric leukemia and this protocol includes children over the age of 2 years.

17.2 Privacy

It is the responsibility of the Research Staff to ensure that protocol patients have received the Center's Notice of Privacy Practices. If the subject has not already done so, MSK personnel must try to obtain acknowledgment before the patient participates in this study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described

in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.3 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered to the Institutional SAE Manager (307 East 63rd Street, 1st Floor) containing the following information:

Fields populated from the CRDB:

- Subject's name
- Medical record number
- Disease/histology (if applicable)
- Protocol number

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form
  - A courtesy copy of the report will be sent to Genzyme to the attention of the Clinical Safety Department at 800-732-8499.

The PI's signature and the date it was signed are required on the completed report.

18.1 Informed consent procedures

Patients potentially eligible for this trial will be informed about the nature of their disease and the standard treatment options will be discussed. Enrollment in this trial will be offered and the rationale and potential risks involved with this treatment program, including risks associated with the various agents and procedures, will be explained. A written informed consent form reiterating these points will be provided for review. Patients wishing to enroll will be required to sign three copies of the consent form; one will be returned to the patient, one will be filed in the patient's chart, and one copy will be filed with the Office of Clinical

Research. Individuals authorized to obtain written consent include Attending Physicians from the Lymphoma Service listed in Section 15.

18.2 Research Authorization

Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, investigators and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate set of signatures from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

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Appendix 1
DATA COLLECTION FORM SCHEDULE

FORM	BASELINE	CYCLE	OFF STUDY	WHEN APLICABLE
Demographic, Disease, Med. History, Prior Treatments	**X**			
Pathology Reports	**X**			
Radiology Reports	**X**			
Treatment and Treatment Modification Form		**X**	**X**	
Physical Exam ((incl.. height, weight, and vitals, ECOG0	**X**	**X**	**X**	
Laboratory Form and Original Reports	**X**	**X**	**X**	
Toxicity Form		**X**	**X**	
Concomitment Medication Form	**X**	**X**	**X**	
Hospitalization Form				**X**
Patient Status and Outcome Form				**X**

Schedule:

Baseline: Forms to be submitted within two weeks of registration

Cycle: To be completed after each cycle and submitted every 4 weeks

Off-Study: To be submitted within 4 weeks of the protocol completion.

Please submit forms to:

Hanna Weissbrot, Research Study Assistant
Memorial Sloan Kettering Cancer Center
633 3rd Avenue, 15th Floor
New York, NY 10017
Fax: 212-557-0787
weissbrh@mskcc.org