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Protocol ID	2015-0117
Protocol Title	A Phase II Trial to Assess the Efficacy and Toxicity of SGI-110 with DLI for the Treatment of AML or MDS Relapsing After Allogeneic Stem Cell Transplantation
Protocol Version	12
Version Date	January 17, 2019
Protocol PI	Betul Oran, MD
Department	Stem Cell Transplantation and Cellular Therapy
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Protocol Page

A Phase II Trial to Assess the Efficacy and Toxicity of SGI-110 with DLI for the Treatment of AML or MDS Relapsing After Allogeneic Stem Cell Transplantation 2015-0117

Core Protocol Information

Short Title	SGI-110 with DLI for AML or MDS Relapsing Post AlloSCT
Study Chair:	Betul Oran
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Full Title:	A Phase II Trial to Assess the Efficacy and Toxicity of SGI-110 with DLI for the Treatment of AML or MDS Relapsing After Allogeneic Stem Cell Transplantation
Public Description:	The goal of this clinical research study is to learn if giving donor lymphocyte cells and SGI-110 will help control acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) (including Chronic Myelomonocytic Leukemia [CMML]) in patients who have had an allogeneic stem cell transplant (using someone else's stem cells) and have relapsed (the disease has gotten worse). Researchers also want to find out if giving SGI-110 after allogenic stem cell transplant in high risk AML and MDS patients would help to improve how long they may remain in remission (free of disease) after transplant. Researchers also want to learn if SGI-110, when given as maintenance therapy for high-risk AML and MDS patients, will reduce the risk of relapse after an allogenic stem cell transplantation. The safety of this treatment will also be studied.
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Activated 01/25/2019
Version:	12
Submitted by:	Peggy S. LeCompte--1/17/2019 5:14:04 PM
OPR Action:	Accepted by: Otisia M. Holiday -- 1/23/2019 1:43:46 PM

Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary Objective

The primary objectives of the study are:

1.1.1 The primary objective of the study is to determine the complete response (CR) rate of SGI-110 with or without donor lymphocyte infusion (DLI) either for the treatment of morphologic relapse or the presence of MRD in patients with acute myeloid leukemia or myelodysplastic syndrome after hematopoietic stem cell transplantation in patients with AML and MDS (cohort 1 and 2).

1.1.2 The primary objective of the study is the relapse-free survival with the use of SGI-110 as maintenance therapy in patients with high risk acute myeloid leukemia or myelodysplastic syndrome after hematopoietic stem cell transplantation (cohort 3).

1.2. Secondary Objectives

The secondary objectives of the study are:

1.2.1 To determine the safety and toxicity of SGI-110 with or without DLI in this subject population.

1.2.2 To evaluate overall response and survival.

1.3 Study Endpoints

1.3.1 Primary Endpoint

The primary endpoint is the CR rate of SGI-110 after enrollment to the clinical trial for cohorts 1 and 2. The primary endpoint is relapse free survival for cohort 3.

1.3.2 Secondary Endpoints

The secondary endpoints are:

1.3.2.1 Safety (type, frequency, severity of AEs and relationship of AEs to SGI-110)

1.3.2.2 Overall response rate

1.3.2.3 Duration of remission

1.3.2.4 Incidence of acute and chronic graft versus host disease (GVHD)

1.3.2.5 Overall survival and disease free survival at one year after study enrollment

2.0 Background

Relapse is the major cause of treatment failure after allogeneic hematopoietic transplantation for AML or MDS (1, 2) and is associated with a dismal prognosis (3). Treatment options for those patients are mainly restricted to chemotherapy, donor lymphocyte infusion (DLI) or second allo-HSCT(4-7). However, remission induction by chemotherapy is challenging because of low response rated and high toxicity (4).

A promising strategy is administration of hypomethylating agents with donor lymphocyte infusion to augment graft-vs-leukemia effects. Hypomethylating agents have direct antileukemia effects and may also favorably modulate GVL activity. We and others have reported the activity of 5-Azacytidine for relapse after allo-HSCT(8). Recently, the safety of 5-Azacytidine in combination of DLI as first salvage therapy for relapse after allo-HSCT in AML/MDS patients have been shown (9).

SGI-110 is a promising agent for AML and MDS The active metabolite of SGI-110, a dinucleotide, is decitabine. SGI-110 is resistant to modification by cytidine deaminase, a

common pathway of decitabine metabolism and deactivation. Therefore SGI-110 delivers decitabine with a 4-fold longer decitabine half-life and overall exposure up to 8 hours. Initial studies have demonstrated relatively high response rates compared to azacitidine and decitabine. In a phase I study, biologically effective dose (BED) was determined to be 60 mg/m2 Days 1-5. A recent phase II study in relapsed/refractory or treatment naïve older AML patients, overall response rate (including CR+CRp+CRi) was 25.6% and 29.8% in 60 mg/m2 and 90 mg/m2 dose groups respectively. These early results confirmed the clinical efficacy of SGI-110 in AML patients. There has been data that hypomethylating agents may increase the immunogenicity of AML blasts by re-expression of important antigens(10-12). Furthermore, animal studies suggest an immunomodulatory role of hypomethylating agents that might attenuate GVHD after DLI(12, 13).

Early intervention is important for treatment of relapse post transplant. The best opportunity to improve outcomes would be to identify relapsing patients with minimal residual disease (MRD) which has been shown to predict impending hematologic relapse(14, 15).

In the current study, we aim to investigate the use of SGI-110 in combination with DLI for morphologic relapse and presence of MRD in the post allo-HSCT setting.

It is well known that most relapses tend to occur within a year after transplant and the prognosis is poor. Because of this short interval before relapse, it is imperative to focus on post transplantation pharmacologic interventions to reduce the relapse risk. The National Cancer Institute proposed strategies to prevent relapse at its *Second International Workshop on the Biology, Prevention, and Treatment of Relapse After Hematopoietic Stem Cell Transplantation* (16). Strategies include improving the conditioning regimen by incorporating new drugs with stronger antileukemia activity and/or less toxicity, graft manipulation, pre-emptive treatment based on detection of minimal residual disease (MRD), early withdrawal of immunosuppression, and maintenance therapy.

There have been studies investigating the role of maintenance therapy in the post-transplant setting to improve relapse incidence. The ideal agent for maintenance therapy would have to fulfill a number of requirements (16). It should be active against the disease being targeted, have acceptable nonhematologic toxicity so that it is tolerated by the patient early after transplant, and have tolerable or preferably no myelotoxicity. In addition, the ideal agent should be able to be given early after transplant, have manageable drug interactions, should not inhibit the graft-versus-tumor effect (GVT), and should not worsen graft-versus-host disease (GVHD). A number of agents are being tested as candidates for maintenance therapy after transplant.

Azacytidine is a DNMT (DNA methyltransferase) inhibitor that has in vitro and in vivo demethylating effects. Since its approval by the U.S. Food and Drug Administration on May 19, 2004, several studies published have shown that DNMT inhibitors have significant anti-tumor activity even after HSCT when patients relapsed, with a 20%-40% complete response (CR) rate (8,17). These findings led to a phase 1 dose-finding study of azacitidine in the post-transplant setting, in which 90 patients were enrolled, but only 45 high-risk patients were actually treated with maintenance therapy. In this trial, median age of the patients was 60 years, and 67% of the study cohort had active disease at transplant (18). The investigators used a Bayesian adaptive method to determine the best dose and schedule combination based on time to toxicity with azacitidine. They tested subcutaneous azacitidine at 8, 16, 24, 32, and 40 mg/m2 and showed that the ideal combination dose was 32 mg/m2 given for 5 consecutive days every 28 days. They gave the drug for 4 cycles, which was chosen arbitrarily. In that study, investigating the safety and efficacy of maintenance therapy for the first time in AML after HSCT, 1-year

event-free survival (EFS) was 58% and 1-year overall survival (OS) was 77%. Twenty-seven percent of patients had grade II-III acute GVHD, and 37% had chronic GVHD. Interestingly, the incidence of chronic GVHD did not decrease with azacitidine dose but with the number of cycles. The investigators concluded that azacitidine at 32 mg/m2 given for 5 days every 28 days for at least 4 cycles was safe in heavily pretreated AML and MDS patients as posttransplant maintenance.

RICAZA study Investigators conducted a study using subcutaneous azacitidine in 27 AML patients who had undergone reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (19). The conditioning regimen was fludarabine, melphalan, and alemtuzumab, and the azacitidine regimen consisted of 36 mg/m2 for 5 consecutive days every 28 days for up to 10 cycles. The median time to start of azacitidine treatment was 64 days after the allogeneic stem cell transplantation. An additional 19 patients enrolled as the control group, received the same conditioning regimen, but no maintenance therapy. The investigators found that 3 of the 27 patients who received maintenance therapy developed grade 2 acute GVHD, and none developed grade 3e4 GVHD. Two patients developed limited chronic GVHD of the skin, and none developed chronic extensive GVHD. In comparison, the control group had a higher GVHD rate, with 7 of 19 developing grade 2 acute GVHD and 7 of 19 chronic GVHD. Despite these encouraging results, 7 of the 27 patients relapsed at a median of 6 months after transplantation.

Decitabine is another epigenetic therapy that has been investigated in the post-transplant maintenance setting (20). The maximum tolerated dose (MTD) was defined as the maximum dose at which $\leq$ 25% of people experience dose-limiting toxicities during the first cycle of treatment. Twenty-four patients were enrolled and 22 were evaluable. All 4 dose levels were completed and no MTD was reached. Overall, decitabine maintenance was well tolerated. Grade 3 and 4 hematological toxicities were experienced by 75% of patients, including all patients treated at the highest dose level. Nine patients completed all 8 cycles and 8 of them remain in CR. Nine patients died from relapse (n = 4), infectious complications (n = 3), and GVHD (n = 2). Most occurrences of acute GVHD were mild and resolved without interruption of treatment; 1 patient died of acute gut GVHD. In conclusion, decitabine maintenance is associated with acceptable toxicities when given in the post-allo transplantation setting.

Despite the encouraging results reported, pre-emptive strategies, to prevent relapse, including pharmacological, immunological and cellular therapies pose the dilemma of administering potentially toxic therapy without evidence of relapse. Therefore patient selection for the right group of patients to be included in those studies is very important.

We previously published that proper risk assessment with the use of minimal residual status at allogeneic stem cell transplantation in combination with cytogenetics and molecular data could overcome this potential problem (21). In our published study, we had shown that even patients transplanted in complete remission, had 1- year relapse incidence higher than 40% if they had adverse risk characteristics by cytogenetics and molecular studies defined as European LeukemiaNet (22) or if they had intermediate risk characteristics with presence of minimal residual disease at stem cell transplantation. In contrast patients without those high risk features had 1-year relapse incidence <10% and they may not need maintenance treatment beyond allogeneic stem cell transplantation.

Therefore, we also aim to investigate the tolerability and efficacy of SGI-110 as post-transplant maintenance treatment in high risk AML and MDS patients (cohort 3).

2.1 General Information

The active metabolite of SGI-110 (2'-deoxy-5-azacytidylyl-(3'·5')-2'-deoxyguanosine sodium salt), a dinucleotide, is decitabine. SGI-110 is resistant to modification by cytidine deaminase, a common pathway of decitabine metabolism and deactivation. The molecular weight of SGI-110 and decitabine are 580 Da and 228 Da, respectively. Therefore, the molar equivalent dose of 1 mg of decitabine is approximately 2.5 mg of SGI-110. SGI-110's activity was demonstrated with the same preclinical pharmacodynamic assays used to demonstrate decitabine's efficacy e.g,, re-expression of p15, p16, and MLH1 and induction of fetal hemoglobin, in vivo. In xenograft studies, SGI-110 demonstrates promising preclinical activity in both hematologic and solid tumors.

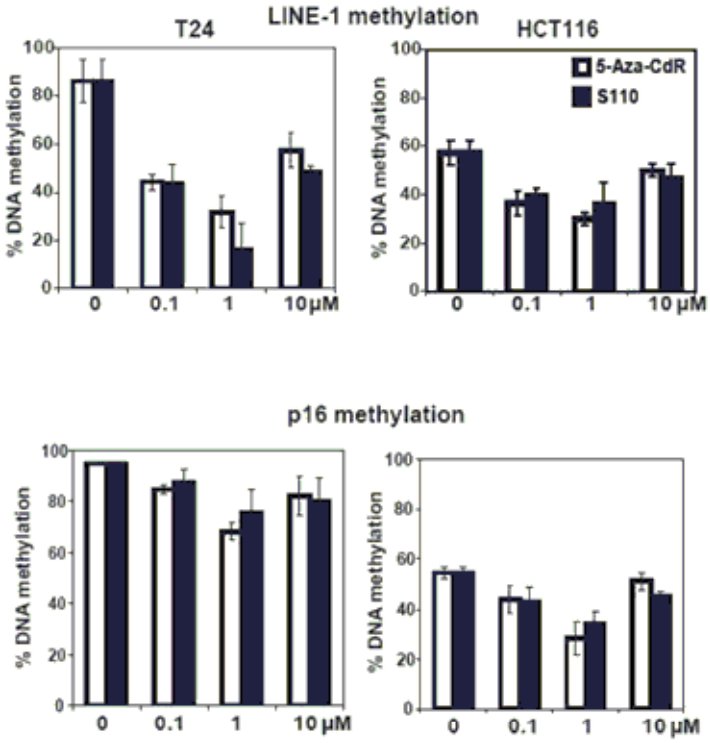
In vitro evidence suggests that SGI-110 has a longer half-life than decitabine in the presence of cytidine deaminase. Exploratory preclinical studies demonstrate that unlike decitabine, SGI-110 can suppress the polycomb repressor complex 2 which is involved in silencing tumor suppressor genes. These promising observations suggest that SGI-110 has improved pharmaceutical properties and biological activities that expand on decitabine's current clinical utility. SGI-110 has shown to be better tolerated in mice than decitabine and is as effective in vivo in inducing p16 expression, reducing DNA methylation at the p16 promotor region, and retarding EJ6 human bladder cancer tumor growth in athymic mice.

2.2 Summary of Nonclinical Data

2.2.1 In Vitro Pharmacology

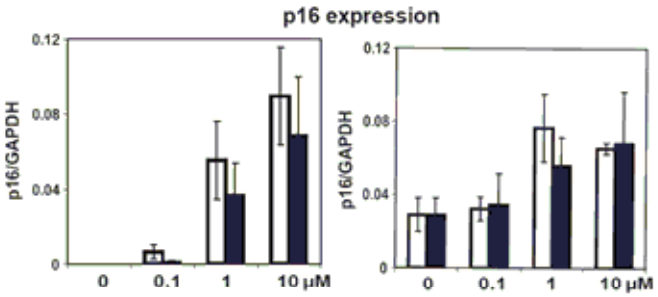
The ability of SGI-110 to change global methylation status was tested by determining the methylation level of long interspersed nucleotide element-1 (LINE-1) and p16 sequences (Figure 1). Repetitive DNA elements, such as LINE-1 retro-transposable elements, serve as useful markers of genome-wide methylation changes and have previously been shown to be demethylated upon treatment with SGI-110 or decitabine (5-Aza-CdR). Both azacitidine and decitabine by itself have low objective response rates.

Figure 1: Effects of SGI-110 (filled bars) and decitabine (open bars) on LINE-1 and p16 Gene Methylation Levels in T-24 and HCT116 Cell Lines



In both T-24 and HCT116 cells, the decrease in the level of methylation was dose-dependent and comparable for SGI-110 and decitabine after 0.1 mM and 1 mM treatment (Figure 1). In the figure noted above and any subsequent places in this document, S110 is the same as SGI-110. At 10 mM concentrations, only a small decrease in methylation was noted, probably due to side effects of high drug concentrations. In fact, 10 mM treatments may be too cytotoxic for effective demethylation to take place as the plating efficiency of T-24 cells indicates. It is well-established that the cytotoxic dose of these demethylating agents is not ideal for optimal epigenetic therapy, since these drugs inhibit DNA methylation best at low doses in cell lines as well as in the clinic. Next, the changes in a methylation-silenced tumor suppressor gene, p16 were assayed in both cancer cell lines.

Figure 2: Effects of SGI-110 (filled bars) and decitabine (open bars) on p16 Gene: Expression Levels in T-24 (left) and HCT116 (right) Cells

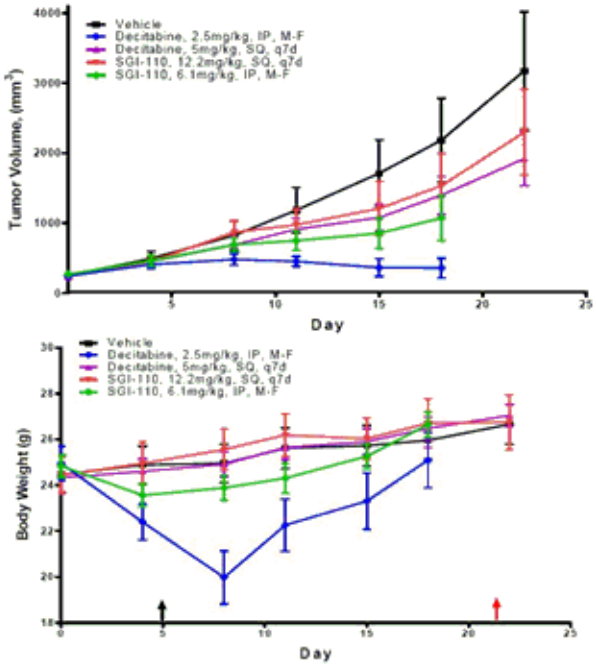


As shown in Figure 2, untreated T-24 bladder carcinoma cells do not express p16, and dose dependent increases in p16 expression were observed after 6 days of continuous treatment with SGI-110 or decitabine. After HCT116 colorectal carcinoma cells were treated for six days, a dose dependent increase in p16 expression was observed with both SGI-110 and decitabine.

2.2.2 In Vivo Pharmacology

The efficacy and safety of SGI-110 was evaluated in several solid tumor models and HL-60 promyelocytic leukemia in comparison to equivalent doses of decitabine (Astex Pharmaceuticals , Inc., data on file). Female nu/nu mice were implanted subcutaneously with HL-60 cells. Animals with exponentially growing tumors were randomized into 5 groups of 8 animals each to include vehicle, SGI-110 5 mg/kg administered subcutaneously every 7 days and 2.5 mg/kg administered intraperitoneally Monday to Friday. Equivalent doses and schedules of decitabine 12.2 mg/kg and 6.1 mg/kg, respectively, were administered subcutaneously for comparison. Results from this study are shown in Table 1 and Figure 3. Both SGI-110 and decitabine demonstrated equivalent antiproliferative activity when administered subcutaneously. When dosed intraperitoneally, SGI-110 seemed to have a greater effect but at the expense of higher toxicity as evidenced by more weight loss and death of 1 animal in the decitabine group.

Figure 3: SGI-110 and SGI-110 Activity and Body Weight Loss in HL-60 Promyelocytic Leukemia



2.3 General Safety (Cardiac, CNS, and Respiratory)

SGI-110 was tested to examine the in vitro effects on the human ether-a-go-go related gene (hERG) potassium channel current. Whole cell patch clamp recordings were made on human embryonic kidney (HEK293) cells that were stably transfected with hERG cDNA. SGI-110 was tested at 10 mM and 300 mM.

SGI-110 inhibited hERG current by 1.4 ± 0.3% (mean ± SEM) at 10 mM and by 1.0 ± 1.3% 300 mM. The half maximal inhibitory concentration (IC50) for the inhibitory effect of SGI-110 on hERG current was not calculated but was estimated to be greater than 300 mM.

The potential neurobehavioral toxicity of SGI-110 was studied after a single subcutaneous dose of SGI-110 (0, 5, 10, and 20 mg/kg) in 2 repeat dose GLP toxicology studies in rats. Functional Observational Battery (FOB) evaluations were conducted on 10 main study animals/group pre-dose (Day -1) and 1 hour post-dose on Day 1 of the study [23] [24]. There were no SGI-110 related changes in any of the FOB measurements in either study. The no-observed-adverse-effect level (NOAEL) of SGI-110 on neurobehavioral function is 30 mg/kg. The potential effects of SGI-110 on respiratory function were studied in a GLP study in rats. Pulmonary function (respiratory rate, tidal volume, and minute volume) were monitored continuously on 8 animals/sex/group for at least 1 hour pre-dose and at least 4 hours post-dose. Test article or vehicle was administered to all groups via a single subcutaneous injection (0, 15, 30, and 60 mg/kg) SGI-110 did not produce mortality and had no effect on clinical signs, respiratory rate, tidal volume, and minute volume. With respect to the basic pulmonary endpoints evaluated in this study, a no-observed-effect-level (NOEL) of at least 60 mg/kg has been established for SGI-110.

2.4 Summary of Clinical Data

For the most updated clinical data, please refer to the most recent Investigators' Brochure. In a Phase I study, 78 patients (64 AML, 14 MDS) were enrolled in the dose escalation part: 44 patients in the daily x 5 regimen and 34 in the weekly x 3 regimen. There median age was 69 years. Median number of prior regimens was 3.

The PK profile demonstrated efficient conversion of SGI-110 to decitabine as predicted from the SGI-110 rational design, resulting in longer decitabine exposure window (beyond 8 hours) compared to Dacogen IV (3-4 hours). At SGI-110 dose range of 60-125 mg/m2, observed mean decitabine AUCs (88-231 ng*hr/mL) reach or exceed the therapeutic range seen with 20 mg/m2 Dacogen IV (115 ng*hr/mL) while achieving only a small fraction of the Cmax (26-64 ng/mL vs 146 ng/mL for Dacogen IV). The effective half-life for decitabine after subcutaneous SGI-110 injection appeared to be prolonged (up to 4-fold or~2.4 hours) compared to Dacogen IV (0.58 hrs). SGI-110 exposures (AUC) increased in a dose proportional manner regardless of the regimen and no accumulation was observed.

Dose-related LINE-1 hypomethylation was observed in patients treated with the daily regimen between 18 and 60 mg/m2; a plateau in maximum average hypomethylation (~25%) was evident at higher daily doses (90-125 mg/m2) and therefore the BED for the daily x 5 schedule is established at 60 mg/m2. The 25% average hypomethylation of LINE-1 compares favorably with that observed historically after Dacogen IV at the dose of 20 mg/m2 daily x 5. The extent of LINE-1 hypomethylation after weekly x 3 SGI-110 was inferior as the maximum average hypomethylation plateaued at ~8% from baseline.

Starting at 36 mg/m2 daily and 60 mg/m2 weekly (44 AML, and 7 MDS patients), clinical responses were observed: 2 CRs, 1 CRp, and 1 CRi in heavily pretreated AML patients; 1 mCR and 1 HI in MDS patients previously treated with azacitidine. All responses were in patients who achieved >10% LINE-1 hypomethylation. The most common adverse events (AEs), regardless of relationship to SGI-110, were diarrhea (21%), febrile neutropenia (17%), fatigue/injection site pain/nausea at 15% each. The most common drug-related AEs were injection site pain (15%), fatigue (8%), nausea (6%), and thrombocytopenia (5%). The MTD was not reached with the weekly regimen up to 125 mg/m2 weekly x 3. With the daily regimen, 125 mg/m2 daily x 5 resulted in 2 dose-limiting toxicities (DLTs) of febrile neutropenia in 3 MDS patients (1 associated with bacteremia, and the other with sepsis and thrombocytopenia Grade 4) while none of the 9 patients with AML had DLT at that dose (14). Since the abstract publication, maximum hypomethylation was noted at the 60 mg/m2 dose, while clinical MTD was defined at 90 mg/m2 dose. Therefore the Phase II study proceeded to compare 60 versus 90 mg/m2 daily for 5 days in newly diagnosed MDS and AML. A further arm investigated SGI-110 60 mg/m2 daily x 10 days in AML salvage. Finally SGI-110 60 mg/m2 daily x 5 is being evaluated in patients with MDS and progression on azacitidine/decitabine therapy.

The Phase II randomized study of the biologic effective dose 60 mg/m2 daily x 5 and clinical Phase II dose 90 mg/m2 daily x 5 is ongoing. As of June 30, 2013, sixty-seven patients (50 relapsed/refractory AML, 17 treatment naïve elderly AML) were treated and had a minimum follow up of 3 months. Patients were randomized to either 60 mg/m^2 dose (32 patients) or 90 mg/m^2 dose (35 patients). The median age was 66 years (range, 22–84), 69% were male, and ECOG PS of 0/1/2 was reported in 11/47/9 patients respectively. Median number of prior regimens was 2 (range, 0–10). Patients' characteristics were well balanced between the 2 dose groups. The primary endpoint of overall remissions (CR, CRp, or CRi) was observed in 17/67 patients (25% with 95% CI, 16–37%). There were 8 complete remissions (CR, CRp, or CRi) in 50 patients with relapsed/refractory AML (16% with 95% CI, 7-29%); and 9 complete remissions

(CR, CRp, or CRi) in 17 treatment-naïve elderly AML patients (53% with 95% CI, 28-77%). Five patients (4 relapsed/refractory, and one treatment-naïve elderly AML) subsequently received a stem cell transplant. There was no difference in the complete remission rate between 60 and 90 mg/m^2 doses (8 remissions in 32 patients at 60 mg/m^2, and 9 remissions in 35 patients at 90 mg/m^2). LINE-1 DNA methylation data before and after treatment was available in 50 (75%) patients enrolled. LINE-1 demethylation · 10% post treatment was observed in 83% and 78% in the 60 mg/m^2 and 90 mg/m^2, respectively. The median maximum LINE-1 demethylation for responders is 25% as compared to 19% for non-responders. The most common adverse events (AEs) regardless of relationship to SGI-110 >/= Grade 3 include febrile neutropenia, thrombocytopenia, anemia, leukopenia, neutropenia, and pneumonia. The 90 mg/m2 dose showed a greater frequency of Grade 3/4 related AEs >/= 10% (anemia, febrile neutropenia, leukopenia, neutropenia, and thrombocytopenia) compared to the 60 mg/m2 dose (15).

2.5 Risks of SGI-110 Based on Early Clinical Data

For the most up-to-date clinical safety information, please refer to the most recent Investigators' Brochure.

The most common risks of SGI-110 are similar to decitabine. These include myelosuppression (neutropenia, febrile neutropenia, thrombocytopenia, and anemia) and its consequences such as fever, infection, sepsis, bacteremia, or bleeding. While in GLP toxicity studies with SGI-110 subcutaneous injections, no adverse local site reactions were noted in the multiple-dose rat and rabbit studies, clinical data indicate injection site pain, irritation, or inflammation in approximately 15% of patients. Local pain seems to be ameliorated by the use of ice packs before or after injection, injecting SGI-110 slowly instead of a push, and carefully avoiding intradermal injections.

2.6 Potential Benefits of SGI-110

Astex Pharmaceuticals has synthesized more stable and potent inhibitors of DNA methylation than decitabine, and demonstrated that short oligonucleotides containing an azapyrimidine effectively inhibit DNA methylation in living cells. SGI-110 was synthesized by coupling decitabine and guanosine into a dinucleotide in an attempt to improve the biological stability and thereby increase the in vivo efficacy of decitabine. Unlike decitabine, SGI-110 initially is resistant to deamination by cytidine deaminases until it is converted into decitabine as a result of cleavage of the phosphodiester linkage by phosphodiesterases.

As such, decitabine is the active metabolite of SGI-110. SGI-110 is a new chemical entity that may possess enhanced pharmacokinetic or pharmacodynamic properties compared to decitabine.

The activity of SGI-110 was demonstrated with the same preclinical pharmacodynamics assays used to demonstrate the activity of decitabine, e.g., re-expression of p15, p16, and MLH1 and induction of fetal hemoglobin, in vivo. In vivo data demonstrate interspecies differences with respect to absorption, distribution, and conversion to decitabine. In xenograft studies, SGI-110 demonstrates promising nonclinical activity in hematologic malignancy and solid tumors.

As such, SGI-110 is an agent that holds promising activity in hematological malignancies given decitabine's proven activity in MDS and AML. The dosage form of SGI-110 developed for use in this study as a subcutaneous injection has the potential for a more sustained release effect

compared to an IV short infusion which, in addition of being more convenient, may prolong efficacy, lower toxicity and change the PK in a beneficial way.

2.7 Potential Benefits of DLI

Although the mechanism by which DLI results in clinical responses is unclear, it is presumed to be a T cell-mediated process. Further analysis of larger numbers of patients is critical to fully understand the mechanisms involved in this response.

Some data suggest that DLI normalizes the T cell receptor (TCR) repertoire and expands the antileukemic cell population. In one study, for example, the TCR repertoire was analyzed before and after DLI among four patients with relapsed chronic myeloid leukemia (CML) and 10 normal controls (25). Initially, the patients' repertoire was characterized by a large number of oligoclonal and clonal patterns, while all controls had a polyclonal pattern. Following infusion of CD4+ lymphocytes, these abnormal patterns slowly normalized over the ensuing several months; by one year, all four patients had an almost normal TCR repertoire. In each patient, expansion of at least one TCR subfamily coincided with the time of disappearance of Philadelphia chromosome-positive cells.

These findings provide evidence of clonal expansion of allogeneic T cells that may be selective mediators of the antileukemic effect. In another study, patients with relapsed CML responding to DLI generated potent antibody responses to CML-associated antigens, suggesting the development of coordinated T and B cell immunity (26).

2.8 Efficacy of DLI

The efficacy of donor lymphocyte infusion (DLI) varies with the underlying malignancy, the dose of infused lymphocytes, and the degree of host lymphodepletion. Outcomes are best for patients with chronic phase chronic myeloid leukemia (CML) followed by patients with lymphoma, multiple myeloma, and acute leukemia (mostly acute myeloid leukemia). Initial studies also suggest that the presence of host-derived regulatory T cells decreases the antitumor effect (28). Patients who respond to DLI will usually demonstrate a clinical response within two to three months, but a full response may take one year or longer(14). Responses can be durable with reports of responses lasting up to 20 years.

Data regarding the efficacy of donor lymphocyte infusions (DLI) come primarily from small case series and two large retrospective studies from Europe and North America:

- The European Group for Blood and Marrow Transplantation reported the results with DLI obtained from 84 patients with chronic myeloid leukemia (CML), 23 with acute myeloid leukemia (AML) and 22 with acute lymphoblastic leukemia (ALL) (29). In this retrospective analysis, 73 percent of patients with relapsed CML had a complete remission after DLI. Remissions, whether defined by molecular or hematologic criteria, were durable. Patients with AML and ALL did not respond as well, as only 29 and zero percent developed a complete remission, respectively. DLI treatment was associated with substantial toxicity: 41 percent developed clinically significant GVHD; 41 percent suffered from myelosuppression; and 13 percent died of causes other than their underlying malignancy.

- A second retrospective analysis (from 25 North American programs) reported the outcomes after DLI in 140 allogeneic transplant patients who relapsed (30). A response rate of 60 percent was observed for patients with CML. The responses were superior in patients with

only cytogenetic relapse or for those treated with DLI while in chronic phase, compared with those who had progressed to either accelerated or blast phases. As in the European study, the results were not as favorable among patients with AML or ALL (15 and 18 percent complete response, respectively). Complications included GVHD (60 percent) and pancytopenia (19 percent).

The decreased response of relapsed acute leukemia to DLI may be due to the more rapid proliferative capacity of malignant cells, since a full response to DLI often requires months. As a result, some clinicians have advocated the use of chemotherapy to first debulk the disease prior to DLI (31). Other clinicians have advocated the use of DLI in patients with acute leukemia and minimal residual disease following HCT (32). As examples:

- In one study, 57 patients with AML, CML, or myelodysplastic syndrome (MDS) relapsing after allogeneic transplant received cytarabine-based chemotherapy, followed by G-CSF-primed DLI without prophylactic immunosuppression (31). Toxicity was appreciable, with a 56 percent incidence of GVHD; treatment-related mortality and two-year overall survival rates were 23 and 19 percent, respectively. Multivariate analysis indicated that those with a post-transplant remission of ·6 months had a relative odds of remission following this treatment approach of 3.7 (95% CI: 1.1-12). Patients with a complete response or no response to this treatment had one-year survival rates of 51 and 5 percent, respectively.
- In another study, 814 patients with standard-risk AML, ALL, or MDS who received allogeneic HCT in first or second complete remission were assessed for minimal residual disease (MRD) to determine eligibility for prophylactic DLI (32). Patients with MRD were eligible for DLI if they had a donor available and had no evidence of active GVHD (56 patients). Patients with MRD who did not have a donor were treated with interleukin-2 (IL-2, 49 patients). When compared with IL-2, DLI resulted in superior rates of disease-free (56 versus 24 percent) and overall (58 versus 28 percent) survival at three years. This compared to rates of disease-free and overall survival at three years of 62 and 66 percent, respectively, in patients with no evidence of MRD after HCT.
- In another study, the combination of azacitidine and donor lymphocyte infusions (DLI) as first salvage therapy for relapse after allogeneic transplantation (allo-HSCT) was studied in 30 patients with acute myeloid leukemia (AML; n=28) or myelodysplastic syndromes (MDS; n=2) within a prospective single-arm multicenter phase-II trial (33). Treatment schedule included eight cycles azacitidine (100 mg/m(2)/day, days 1-5, every 28 days) followed by DLI (from 1-5 × 10(6) to 1-5 × 10(8) CD3(+)cells/kg) after every second azacitidine cycle. A median of three courses azacitidine (range 1-8) were administered, and 22 patients (73%) received DLI. Overall response rate was 30%, including seven complete remissions (CRs, 23%) and two partial remissions (7%). Patients with MDS or AML with myelodysplasia-related changes were more likely to respond (P=0.011), and a lower blast count (P=0.039) as well as high-risk cytogenetics (P=0.035) correlated with the likelihood to achieve CR. Incidence of acute and chronic graft-versus-host disease was 37% and 17%, respectively.

The authors updated their and reported the retrospectively analyzes f 154 patients with acute myeloid leukemia (AML, n = 124), myelodysplastic (MDS, n = 28), or myeloproliferative syndrome (n = 2) (34). All patients received a median number of 4 courses of Aza (range, 4 to 14) and DLI were administered to 105 patients (68%; median number of DLI, 2; range, 1 to 7). Overall survival (OS) at 2 years was 29% ± 4%. Molecular-only relapse (HR, .14; 95% CI, .03 to .59; P = .007), diagnosis of MDS (HR, .33; 95% CI, .16 to .67; P = .002), and bone marrow blasts <13% (HR, .54; 95% CI, .32 to .91; P = .021) were associated with better OS.

Accordingly, 2-year OS rate was higher in MDS patients (66% ± 10%, P = .001) and correlated with disease burden in patients with AML. These results suggested that Aza and DLI were effective and well-tolerated treatment option for patients with relapse after allo-HSCT, in particular those with MDS or AML and low disease burden.

Responses to DLI can be remarkably durable. For example, in an analysis of 66 patients with CML who relapsed and received DLI, 67 percent achieved a molecular complete remission (CR) (35). For those patients achieving a molecular CR, 95 percent were alive and in continuous CR at three years following DLI. Similar results have been reported by others (36-38).

3.0 Patient Eligibility

3.1 Inclusion Criteria

- 3.1.1 Diagnosis of Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (including Chronic Myelomonocytic Leukemia [CMML]) according to WHO classification that underwent first allogeneic HSCT with either peripheral blood or bone marrow as the source of the hematopoietic stem cells.
- 3.1.2 Age 18 to 75 years old.
- 3.1.3 No more than 1 antigen mismatch at HLA-A, B, C, DRB1 and DQB1 locus for either related or unrelated donor.
- 3.1.4 High risk AML and MDS patients will be included.
  - 3.1.4.1 Cohort 1: Morphological relapse at least 90 days after stem cell transplant:
    - 3.1.4.1.1 MDS patients: Re-appearance of dysplastic changes in the bone marrow, with or without increase in bone marrow last count, which is pathologically consistent with myelodysplastic syndrome.
    - 3.1.4.1.2 AML patients: Bone marrow blast count >/= 5%.
  - 3.1.4.2 Cohort 2: Persistence or reappearance of minimal residual disease by flow cytometry or cytogenetic or molecular testing while being in morphological remission after allogeneic stem cell transplantation.
  - 3.1.4.3 Cohort 3: High risk AML and MDS patients who are in complete remission morphologically with no evidence of minimal residual disease by flow cytometry or cytogenetic or molecular testing after allogeneic stem cell transplantation.
    - 3.1.4.3.1 MDS patients:
      - 3.1.4.3.1.1 Cytogenetics consistent with poor or very poor risk group by 5-risk classification defined by Schanz, et al (43).
      - 3.1.4.3.1.2 Cytogenetics consistent with monosomal karyotype.
      - 3.1.4.3.1.3 Bone marrow blast count > 5% but less than 20% at any time during their disease course before HSCT.
      - 3.1.4.3.1.4 Peripheral blood blast </=5% at HSCT.
      - 3.1.4.3.1.5 Therapy-related MDS.
    - 3.1.4.3.2 AML patients
      - 3.1.4.3.2.1 Cytogenetics and molecular features consistent with adverse risk group by European LeukemiaNet classification for AML

(see Appendix G.) (22).

3.1.4.3.2.2 Presence of minimal residual disease by multi-color flow cytometry or cytogenetics or molecular studies at the time of HSCT.

3.1.4.3.2.3 Presence of active disease defined as bone marrow blast count >5% but less than </=10% at the time of HSCT.

3.1.4.3.2.4 Peripheral blood blast count </=5% at HSCT.

3.1.4.3.2.5 Therapy-related AML.

3.1.4.3.3 Be able to start the drug therapy between 42 to 100 days following allogeneic SCT.

3.1.4.3.3.1 No more than 1 prior allogeneic SCT.

3.1.4.3.3.2 Post-transplant bone marrow consistent with complete remission with no evidence of minimal residual disease by flow-cytometry or cytogenetics or molecular testing.

3.1.4.3.3.3 Adequate engraftment within 14 days prior to starting study drug:

- ANC >/= 1.0 x 10^9/L without daily use of myeloid growth factor; and,
- Platelet >/= 50 x 10^9/L without platelet transfusion within 1 week.

3.1.5 ECOG performance status of 0, 1, or 2.

3.1.6 Serum creatinine </=1.5 mg/dL or creatinine clearance greater or equal than 40 cc/min as defined by the Cockcroft-Gault Equation*.

3.1.6.1 Males (mL/min):(140-age)*IBW(kg) / 72*(serum creatinine(mg/dl))

3.1.6.2 Females (mL/min):0.85*(140-age)*IBW(kg) / 72*(serum creatinine(mg/dl)).

3.1.7 Serum bilirubin </= 1.5 x upper limit of normal (ULN).

3.1.8 Aspartate transaminase (AST) or alanine transaminase (ALT) </= 2.5 x ULN.

3.1.9 Alkaline phosphatase </= 2.5 x UL.

3.1.10 No active bleeding.

3.1.11 No uncontrolled GVHD.

3.1.12 No clinical evidence of life-threatening infection.

3.1.13 Capable of understanding the investigational nature, potential risks and benefits of the study, and able to provide valid informed consent.

3.1.14 HIV negative and HBs-Ag negative.

3.1.15 Negative serum or urine pregnancy test for women with reproductive potential. The only subjects who will be exempt from this criterion are postmenopausal women (defined as women who have been amenorrheic for > 12 months) or subjects who have been surgically sterilized or otherwise proven sterile.

3.2 Exclusion Criteria:

3.2.1 Use of any anti-leukemic agents after relapse is documented (note that the use of these anti-leukemic agents given as post-transplant maintenance therapy is allowed in this study, e.g., subcutaneous or oral 5-Azacytidine or FLT3 inhibitors for maintenance) for cohorts 1 and 2.

3.2.2 Bone marrow blast count >60% for cohort 1.

3.2.3 Use of any of the following after transplantation and prior to starting study therapy for cohort 3:

3.2.3.1 Investigational agents/therapies.
3.2.3.2 Anti-leukemic agents given as post-transplant maintenance therapy (e.g., subcutaneous or oral 5-Azacytidine or FLT3 inhibitors for maintenance).
3.2.3 Active acute GVHD grade II or higher.
3.2.4 Active chronic GVHD that is extensive.
3.2.5 Concurrent use of systemic immune suppressive other than calcineurin inhibitors and sirolimus.
3.2.6 Active uncontrolled systemic fungal, bacterial or viral infection.
3.2.7 Symptomatic or uncontrolled arrhythmias.
3.2.8 Significant active cardiac disease within the previous 6 months, including:
3.2.8.1 New York Hear Association (NYHA) class III or IV congestive heart failure;
3.2.8.2 Unstable angina or angina requiring surgical or medical intervention, and/or;
3.2.8.3 Myocardial infarction.
3.2.9 Known active viral infection with Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV).
3.2.10 Prior history of solid tumors other than MDS or AML, unless the subject has been free of the disease for >/= 1 year. However, subjects with the following history/concurrent conditions are allowed:
- Basal or squamous cell carcinoma of the skin;
- Carcinoma in situ of the cervix;
- Carcinoma in situ of the breast;
- Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, node, metastasis [TNM] clinical staging system).

4.0 Treatment Plan

4.1 This is a single-arm phase II study to determine the efficacy of SGI-110 with or without DLI either for the treatment of the morphologic relapse or the presence of MRD in patients with acute myeloid leukemia or myelodysplastic syndrome after hematopoietic stem cell transplantation and as maintenance therapy without DLI, given after hematopoietic stem cell transplantation for high risk AML and MDS patients.
There will be three patient subgroups (cohorts):
Cohort 1: Patients with morphological relapse for AML and MDS as defined in Section 3.1.4.1.
Cohort 2: Patients with minimal residual disease as defined in Section 3.1.4.2.
The protocol specific data will be entered into PDMS/CORe, the electronic case report form.
Cohort 3: High risk AML and MDS patients defined in Section 3.1.4.3

The Investigator or physician designee is responsible for providing source documentation and assigning attribution for all AEs.

4.2. Treatment plan of SGI-110 administration (39, 40):

Following confirmation of eligibility, subjects will receive subcutaneous (SC) SGI-110 daily for the first 5 days of each 28-day cycle.

4.2.1. Cohort 1

4.2.1.1 The enrolled patients with morphological relapse will start treatment at the dose level 3 which is 60 mg/m2 SC daily, days 1 to 5. The treatment will be given with an intent to achieve CR. Treatment delays and dose reductions are allowed by discretion of the principal investigator and the treating physician on the basis of tolerability.

4.2.1.2 The response assessments schedule will be as follows:

4.2.1.2.1 The first response assessment will be performed after the second cycle of SGI-110 given prior to initiation of the third cycle.

4.2.1.2.2 For patients who do not achieve CR/incomplete count recovery (CRi) after the second cycle of SGI-110 and continue to receive SGI-110 with an aim to achieve CR, the next assessment will be performed after the fourth cycle.

4.2.1.2.3 For patients who do not achieve CR/CRi after the fourth cycle of SGI-110 and continue to receive SGI-110 with an aim to achieve CR, the next assessment will be performed after the sixth cycle.

4.2.1.2.4 Patients may have an earlier disease assessment rather than the indicated time point in the study protocol at the discretion of the treating physician and principal investigator.

4.2.1.3 Patients who do not achieve CR/CRi within the first 2 cycles of SGI-110 and still have less than 30% bone marrow bone marrow blasts will continue to receive SGI-110 with an intent to achieve CR.

4.2.1.4 Patients who do not achieve CR/CRi within the first 4 cycles of SGI-110 and still have less than 30% bone marrow bone marrow blasts will have the option to receive two more cycles of SGI-110 with an intent to achieve CR if the patient, treating physician and principal investigator determine such an action as the best interest of the patient.

4.2.1.5 Patients who do not achieve CR/CRi after the fourth cycle of SGI-110 will be taken off the study if the patient, treating physician and principal investigator do not determine continuation of SGI-110 for 1-2 more cycles with an intent to achieve CR as the best interest of the patient.

4.2.1.6 Any patient who does not achieve response after a maximum use of six cycles of SGI-110 will be taken off the study.

4.2.1.7 Patients who are reported to achieve CR/CRi at any response assessment time points will continue the study drug, SGI-110, as maintenance therapy at the subsequent treatment cycles.

4.2.1.7.1 The starting maintenance dose will be 40 mg/m2/day (dose level 1) for patients who achieved CR/CRi with doses higher than 40 mg/m2/day.

4.2.1.7.2 The starting maintenance dose will be at least one dose level lower than the treatment dose that led the patient to achieve CR/CRi if the patient was on 40 mg/m2/day dose or less during treatments with active disease.

4.2.1.8 Patients will not be taken off therapy with SGI-110 prior to completion of the first 4 courses unless for unequivocal disease progression while on therapy, unacceptable toxicities, or patient request.

4.2.1.9 During the treatment cycles given with the intent to achieve CR (patient has active disease), the dose of SGI-110 can be decreased at least by

one dose level (presented at Section 4.4.4) at the discretion of the treating physician or principal investigator if:

4.2.1.9.1 There are grade 3-4 reversible non-hematological toxicities attributable to the drug observed.

4.2.1.9.2 Dose change is considered in the best interest of the patient.

4.2.1.10 For patients who achieve CR/CRi, treatment with SGI-110 will be continued as maintenance therapy until treatment failure or for a maximum of 12 cycles of SGI-110 treatment.

4.2.1.11 Treatment with SGI-110 will be stopped at any time point if patients exhibit evidence of treatment failure, disease progression, experience of unacceptable toxicity, or the investigator determines that the discontinuation of treatment is in the patient's best interest as provided in Section 6.0.

4.2.2. Cohort 2: Patients without morphological evidence of relapse but with minimal residual disease.

4.2.2.1 The enrolled patients will start treatment at the dose level 1 which is 40 mg/m2 SC daily, days 1 to 5. Treatment delays up to 70 days are allowed.

4.2.2.2 The response assessments schedule will be as follows:

4.2.2.2.1 The first response assessment will be performed after the second cycle of SGI-110 given prior to initiation of third cycle.

4.2.2.2.2 For patients who have persistency of detectable MRD after the second cycle of SGI-110 and continue to receive SGI-110 the next assessment will be performed after the fourth cycle.

4.2.2.2.3 For patients who have persistency of detectable MRD after the fourth cycle of SGI-110 and continue to receive SGI-110 the next assessment will be performed after the sixth cycle.

4.2.2.2.4 Patients may have an earlier disease assessment rather than the indicated time point in the study protocol at the discretion of the treating physician and principal investigator.

4.2.2.3 If patients still have detectable MRD even after the fourth cycle of SGI-110, further treatment (maximum two more cycles) with SGI-110 will be given only if the patient, treating physician and principal investigator determine such an action as the best interest of the patient.

4.2.2.4 Patients who are documented to have no detectable MRD at any time point while treated with SGI-110 will continue the study drug as maintenance therapy at subsequent cycles after documentation of MRD negative status.

4.2.2.5 The dose level of SGI-110 can be increased at least one dose level at the discretion of treating physician and principal investigator if persistency of MRD is documented at any time point of disease assessment while on study.

4.2.2.6 For patients with detectable minimal residual disease at study entry, treatment with SGI-110 will be continued until treatment failure or for a

maximum of 12 cycles if they have become negative for minimal residual disease at any time point within the first 6 cycles of study drug.

4.2.2.7 Treatment with SGI-110 will be stopped at any time point if patients exhibit evidence of treatment failure, disease progression, experience of unacceptable toxicity, or the investigator determines that the discontinuation of treatment is in the patient's best interest as provided in Section 6.0.

4.2.3. Cohort 3: High risk AML and MDS patients who are in complete remission morphologically with no evidence of minimal residual disease by flow cytometry or cytogenetic or molecular testing after allogeneic stem cell transplantation.

4.2.3.1 The enrolled patients will start treatment at the dose level -1 which is 30 mg/m2 SC daily, days 1 to 5 for each 28-day treatment cycle.

4.2.3.2 Treatment delays up to 70 days will be allowed.

4.2.3.3 The response assessments will be performed per departmental guidelines which is day +100, 6th month, 1- year after allogeneic stem cell transplantation.

4.2.3.4 Disease assessment can be done at any time point after transplantation if it is deemed indicated by the treating physician and/or principal investigator.

4.2.3.5 The dose level of SGI-110 can be increased at least one dose level at the discretion of treating physician and principal investigator if deemed in the best interest of the patient by the treating physician and/or principal investigator.

4.2.3.6 For patients who remain in remission without detectable minimal residual disease at study entry, treatment with SGI-110 will be continued until treatment failure or for a maximum of 12 cycles.

4.2.3.7 Treatment with SGI-110 will be stopped at any time point if patients exhibit evidence of treatment failure, disease progression, experience of unacceptable toxicity, or the treating physician and/or principal investigator determines that the discontinuation of treatment is in the patient's best interest as provided in Section 6.0.

4.2.4 **Cross-over.** Patients treated on cohort #2 (patients with minimal residual disease while in morphological remission and cohort #3 (maintenance treatment cohort) will be allowed to receive higher doses of SGI-110 if they progress while on therapy with the study drug. Patients who are considered for cross-over to another study cohort due to progression of disease with an aim to receive higher doses of SGI-110 will be screened for the eligibility of that study cohort prior to initiation of higher doses of study drug.

4.3 SGI-110 Reconstitution and Administration

See the current Investigator's Brochure Appendix for details.

4.4. SGI-110 Dose Modifications

Subjects will be monitored for hematologic toxicity and non-hematologic toxicity with the National Cancer Institute (NCI) Common Terminology Criteria Adverse Events (CTCAE, Version 4.0) used as a guide for the grading of the severity.

4.4.1 Hematologic Toxicity

4.4.1.1 Cohort 1:

4.4.1.1.1 No dose reductions, delays or modifications are required for hematologic toxicities during the treatment cycles given with an intent to achieve CR/CRi. It is assumed that low counts observed in the presence of active disease (no morphological remission) are due to involvement by the disease and require treatment for improvement. Patients will not require dose modifications for hematological toxicity before they are reported to achieve morphological remission.

4.4.1.1.2 For patients who achieve complete morphological remission (CR/CRi) on study, they will receive the subsequent cycles (given as maintenance therapy) approximately every 28 days, provided that their peripheral blood counts have recovered (ANC>=1.0 X 10^9 /L and platelet count>=50 X 10^9/L)). If the peripheral count recovery is delayed beyond 42 days from Day 1 of the prior cycle and the delay is presumed to be secondary to therapy (after confirmation of achieving morphological remission), the SGI-110 doses may be reduced at least by one level for subsequent doses (e.g. from 40 to 30 mg).

4.4.1.2 Cohort 2:

4.4.1.2.1 No dose reductions, delays or modifications are required for hematologic toxicities during the treatment cycles given in the continuous presence of MRD. It is assumed that low counts in the presence of MRD are due to disease involvement and require treatment for improvement. Indeed, the dose level of SGI-110 can be increased at least one dose level at the discretion of treating physician and principal investigator if persistency of MRD is documented at any time point of disease assessment while on study independent of hematological toxicities observed as indicated at 4.2.2.4.

4.4.1.2.2 After the documentation of MRD negative status with the SGI-110 treatment, if the peripheral count recovery is delayed beyond 42 days from Day 1 of the prior cycle and the delay is presumed to be secondary to therapy, the SGI-110 doses may be reduced at least by one level for subsequent doses (e.g., from 30 to 20 mg).

4.4.1.3 Cohort 3: If the peripheral count recovery is delayed beyond 42 days from Day 1 of the prior cycle and the delay is presumed to be secondary to therapy, the SGI-110 doses may be reduced at least by one level for subsequent doses (e.g., from 30 to 20 mg).

4.4.2 Non-hematological toxicity

4.4.2.1 The dose of SGI-110 will be reduced by one level for grade 3-4 reversible toxicities attributable to the drug independent of the disease status at the

time of ongoing treatment with study drug. If toxicity is still present on next cycle with one dose level reduction, dose will be reduced with one more level again (minimum dose is 20 mg/m2 given for 3 subsequent days). If toxicity is present after 2 dose level reductions, SGI-110 will be discontinued.

4.4.2.2 Dose reduction for grade 2 reversible toxicities and other dose modifications can be implemented if in the best interest of the patient, after discussion with the primary investigator.

4.4.2.3 Infections are not considered drug related toxicity.

4.4.3 Patients with uncontrolled GVHD will not be eligible to receive SGI-110. If GVHD resolves, patients may receive SGI-110 with at least one level dose reduction in the subsequent cycle. If GVHD remains controlled, full dose can be used in the subsequent cycles.

4.4.4 Treatment delays up to 70 days (cohort #2 and #3) are allowed. For cohort #1, treatment delays will be decided by the treating physician or principal investigator based on the tolerability of the drug taken the best interest of the patient into account).

4.4.5 SGI-110 dose levels allowed in the study

- 20 mg/m2 SC, Days 1 through 3 (dose level -3)
- 20 mg/m2 SC, Days 1 through 5 (dose level -2)
- 30 mg/m2 SC, Days 1 through 5 (dose level -1)
- 40 mg/m2 SC, Days 1 through 5 (dose level 1)
- 50 mg/m2 SC, Days 1 through 5 (dose level 2)
- 60 mg/m2 SC, Days 1 through 5 (dose level 3)

4.5 Criteria to receive SGI-110

4.5.1 Criteria to receive the first cycle

4.5.1.1 Serum creatinine </= 1.5 mg/dL or creatinine clearance greater than 40 cc/min as defined by the Cockcroft-Gault Equation.

4.5.1.1.1 Males (mL/min):(140-age)*IBW(kg) / 72*(serum creatinine(mg/dl))

4.5.1.1.2 Females (mL/min):0.85*(140-age)*IBW(kg) / 72*(serum creatinine(mg/dl)).

4.5.1.2 Serum bilirubin </= 1.5 x upper limit of normal (ULN)

4.5.1.3 Aspartate transaminase (AST) or alanine transaminase (ALT) </= 2.5 x ULN

4.5.1.4 Alkaline phosphatase </= 2.5 x UL

4.5.1.5 No active bleeding.

4.5.1.6 No uncontrolled GVHD.

4.5.1.7 No clinical evidence of life-threatening infection.

4.5.1.8 Negative serum or urine pregnancy test for females of childbearing potential. The only subjects who will be exempt from this criterion are postmenopausal women (defined as women who have been amenorrheic for > 12 months) or subjects who have been surgically sterilized or otherwise proven sterile.

4.5.2 Criteria to receive SGI-110 given as maintenance therapy (first cycle of maintenance therapy and beyond for cohorts 1 and 2 and second cycle and beyond for cohort 3). Each cycle is to be started 28-56 days after the previous cycle.

4.5.2.1 ANC >/=1.0 x 10^9 /L without daily growth factor (Intermittent use of growth factor is allowed as clinically indicated and platelet count>=50 X 10^9/L with or without transfusion

4.5.2.2 No clinical evidence of life-threatening infection.

4.5.2.3 No active bleeding.

4.5.2.4 No active uncontrolled GVHD.

4.5.2.5 Serum creatinine < 2 mg/dL.

4.5.2.6 Serum bilirubin < 1.5 mg/dL.

4.5.2.7 ALT </= 200 IU/ml unless related to patient's malignancy.

4.5.2.8 Negative serum or urine pregnancy test for females of childbearing potential. The only subjects who will be exempt from this criterion are postmenopausal women (defined as women who have been amenorrheic for > 12 months) or subjects who have been surgically sterilized or otherwise proven sterile.

4.6 Donor Lymphocyte Infusion (for cohorts 1 and 2)

4.6.1 The patients will receive 3 planned DLI infusions after enrollment to the study if below criteria is met.

4.6.1.1 No active bleeding.

4.6.1.2 No uncontrolled GVHD.

4.6.1.3 Patients should be off concurrent of use systemic immune suppressive other than calcineurin inhibitors and sirolimus.

4.6.1.4 No clinical evidence of life-threatening infection

4.6.1.5 No evidence of autologous reconstitution of the hematopoiesis. Chimerism studies from peripheral blood and/or bone marrow at study entry or at later time points on study will be used to rule out autologous.

4.6.2. Patients will not receive DLI:

4.6.2.1. If criteria summarized under 4.6.1 is not met.

4.6.2.2 Donor is not available

4.6.2.3. The treating physician and the PI think it is in the best interest of the patient not to receive DLI.

4.6.3 For patients eligible to receive the DLI, the first DLI is planned to be given on the 6th day of the second SGI-110 cycle immediately after the completion of the 5 days of SGI-110 administration if no GVHD observed. If the 6th day falls over a weekend day or holiday, the DLI will be given on the very first week day following the 6th day.

4.6.4 Additional DLI will be permitted in patients without uncontrolled GVHD on the 6th day of the 4th and 6th course of SGI-110 at the discretion of the treating physician. If the 6th day falls over a weekend day or holiday, the DLI will be given on the very first week day following the 6th day.

4.6.5 DLI dose:

4.6.5.1 CD3 1 x 10^7/kg for matched related donor; 3 x 10^6/kg for matched unrelated and mismatched unrelated donors.

4.6.5.2 There will be no scheduled dose escalations and CD3+ cells dose of DLI

can be lower at the discretion of the treating physician on subsequent administrations.

4.6.6 Criteria to give DLI
- 4.6.6.1 No active bleeding.
- 4.6.6.2 No uncontrolled GVHD.
- 4.6.6.3 Patients should be off concurrent of use systemic immune suppressive other than calcineurin inhibitors and sirolimus.
- 4.6.6.4 No clinical evidence of life-threatening infection
- 4.6.6.5 No evidence of autologous reconstitution of the hematopoiesis. Chimerism studies from peripheral blood and/or bone marrow at study entry or at later time points on study will be used to rule out autologous reconstitution.

5.0 Evaluation During Study

5.1 Evaluations during SGI-110 cycles

5.1.1 To be done within 72 hours of each cycle and if clinically indicated, on the third day of each cycle and once per week in the second and third week of each cycle: CBC, differential, platelet, SGPT, bilirubin, creatinine, electrolytes, serum or urine pregnancy test for women with reproductive potential.

Other laboratory tests can be performed as medically indicated.

5.2 Evaluations prior to DLI administration

To be done within 72 hours of each cycle and if clinically indicated, on the third day of each cycle and once in the second and third week: CBC, differential, platelet, SGPT, bilirubin, creatinine, electrolytes.

5.3 Response Evaluation:
Disease status evaluations follow standard practice. If clinically indicated, these studies may be done at other time points, which can replace the nearest planned time point.

For cohorts 1 and 2:

5.3.1 To be done after 2nd, 4th, and 6th cycles of SGI-110.

5.3.2 After the patients are documented to achieve response, further disease status evaluation will be performed when it is clinically indicated.

5.3.3 Disease status will include:
- 5.3.1.1 Bone marrow aspirate and biopsy with cytogenetics, FISH, flow and molecular studies.
- 5.3.1.2 Chimerism studies from peripheral blood

5.3.4 If a patient shows no evidence of response in the absence of disease progression after the second cycle of SGI-110 (Day 28 +/-7 days), further bone marrow aspirate and/or biopsy will be scheduled to document response at the end of Cycle 4 (Day 28 +/-7 days).

5.3.5 If a patient shows no evidence of response in the absence of disease progression even after the fourth cycle of SGI-110 (Day 28 +/-7 days), further bone marrow aspirate and/or biopsy will be scheduled to document response at the end of Cycle 6 (Day 28 +/-7 days).

5.3.6 If the patient does not show evidence of response at the end of Cycle 6, the patient

will be taken off the study with no further follow-up.

5.3.7 Bone marrow evaluations and peripheral blood chimerism studies can be ordered more frequently if clinically indicated.

For cohort 3:

5.3.8 Disease status evaluations follow standard practice with day +100, Month 6, and 1-year disease evaluations.

5.3.9 Disease status evaluation will include:

5.3.9.1 Bone marrow aspirate and biopsy with cytogenetics, FISH, flow and molecular studies.

5.3.9.2 Chimerism studies from peripheral blood.

5.4 Outside Physician Participation During Treatment

This will be performed only after the patients are documented to show evidence of response with the therapy (morphological CR for cohort 1 and MRD negative status for cohort 2 respectively). DLI administrations will only be performed at MDACC.

5.4.1 MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.

5.4.2 A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care and perform certain laboratory tests (see Appendix D.).

5.4.3 Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MD Anderson physician, indicating that they have reviewed it.

5.4.4 A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

5.4.5 Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

5.4.6 The home physician will be requested to report to the MDACC physician investigator all SAE’s within 24 hours of documented occurrence.

Communication of protocol required evaluations can be by telephone, fax, or e-mail. Patients will return to MDACC at least every 3 months for evaluation. The Study Chair or treating physician must review the laboratory results, determine clinical significance, and sign and date the report. Concomitant medications will be captured in the electronic medical record.

5.5 Follow-Up Evaluations

Follow-Up evaluations will be performed per AML or MDS standard of care as appropriate.

6.0 Criteria for Response

6.1 Response definition:

6.1.1 For patients with documented morphological relapse at study entry:

6.1.1.1 Clinical response and hematological improvement for patients with myelodysplastic syndrome will be determined according to the 2006 International Working Group recommendations.

6.1.1.1.1 Complete remission (CR): Bone marrow with </= 5% bone marrow blasts with normal maturation of all cell lines; a peripheral blood granulocyte count >/= 1 X 10^9/L and a platelet count >/= 100 x 10^9/L

6.1.1.1.2 Marrow CR: Bone marrow has </=5% myeloblasts and decrease by >/=50% over pretreatment.

6.1.1.1.3 Partial remission (PR): patients must demonstrate all CR criteria if abnormal before treatment except that marrow blasts should decrease by 50% or more compared with pretreatment levels, or patients may demonstrate a less-advanced MDS disease classification category than prior to treatment.

6.1.1.2 Clinical response for patients with acute myeloid leukemia will be based on revised recommendations of the 2003 International Working Group.

6.1.1.2.1 Morphologic complete remission: Bone marrow with <5% blasts in the absence of extramedullary disease in addition to a peripheral blood granulocyte count >/= 1 X 10^9/L and a platelet count >/= 100 x 10^9/L.

6.1.1.2.2 Partial remission (PR): This designation requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.

6.1.1.2.3 Morphological complete remission with incomplete count recovery (CRi): Bone marrow blast count <5%.

6.1.2 For patients with persistent or recurrent disease by molecular, cytogenetic or flow cytometry findings without morphologic remission at study entry; disappearance of leukemia clone by repeat studies.

6.1.3 For cohort 3, response will be remaining in morphological remission without evidence of minimal residual disease by flow-cytometry, cytogenetics or molecular findings.

6.2. No response:

6.2.1 Any response less than a partial response.

6.3 Progression:

6.3.1 For patients with documented morphological relapse at study entry; bone marrow blast count more than 60% and/or new extramedullary sites.

6.3.2 For patients with persistent or recurrent disease by molecular, cytogenetic or flow cytometry findings despite morphologic remission at study entry; evidence of morphologic relapse.

6.3.3 For cohort 3, any disease progression with either morphological relapse and/or

evidence of minimal residual disease with flow-cytometry, cytogenetics or molecular testing.

7.0 Statistical Considerations

This is a single-arm phase IIA activity trial of SGI-110 in combination with or without DLI given post allogeneic stem cell transplant for patients with hematologic malignancies. There will be three patient subgroups, patients with minimal residual disease (MRD), and patients who have relapsed (REL) and patients who receive SGI-110 as maintenance. The phase IIA design of Thall and Sung (41) will be used to monitor the response rate within each subgroup. In the MRD subgroup, response will be defined as resolution of MRD with SGI-110. In the REL subgroup, clinical response to SGI-110 for patients with myelodysplastic syndrome will be determined according to the 2006 International Working Group recommendations and for patients with acute myeloid leukemia will be based on revised recommendations of the 2003 International Working Group. For the maintenance cohort (cohort #3), that will be relapse free survival at 1-year.

Disease and Treatment Regime. This is a single-arm phase IIA activity trial of SGI-110 in combination with or without DLI given post allogeneic stem cell transplant (allosct) for patients with hematologic malignancies. There will be three patient subgroups. The first subgroup will be patients with minimal residual disease (MRD). The second subgroup will be patients who have relapsed (REL). The third group will be high risk patients who will receive the intervention for maintenance. The phase IIA design of Thall and Sung (41) will be used to monitor the response rate within each subgroup. The two differences between the subgroups are in terms of (i) entry criteria and (ii) definition of response.

7.1 Cohort 1 and 2: The same phase IIA design will be used for cohort 1 and 2, as follows: A response probability of .20 or larger will be considered promising. A maximum of 25 patients with will be treated in each group. Accrual will be stopped due to futility if less than or equal to 0/8 or 1/20 responses are observed. A patient may have therapy temporarily postponed for up to 56 days due to toxicity. Any patient whose therapy has been started and later permanently discontinued due to the following will be counted as a treatment failure, that is, a non-responder: 1) progressive disease, or 2) due to death, or 3) dropout, or 4) physician decision that it is futile to continue, or 5) severe toxicity prior to achieving disease remission. Patients who do not complete the first cycle of treatment will be considered as non-evaluable. Secondary outcomes will include disease-free survival (DFS) time, overall survival (OS) time, graft-versus-host disease, safety and duration of remission. Within each subgroup (MRD and REL), these events will be tabulated and the distributions of DFS and OS time estimated using the method of Kaplan and Meier (42).

Patients with MRD. In this subgroup, response will be defined as resolution of MRD, at any time point within the first 6 cycles of SGI-110 treatment. A response probability of .20 or larger will be considered promising. A maximum of 25 patients with MRD will be treated. Denoting $p = Pr(\text{response})$, it will be assumed that p follows a beta(.20, .80) prior. Accrual will be stopped due to futility if $Pr(p > .20 \mid \text{data}) < .02$. This implies that accrual of patient with MRD will be stopped with SGI-110 declared not promising in these patients if less than or equal to 0/8 or 1/20 responses are observed. If necessary, accrual will be suspended after 8 or 20 patients have been treated in order to apply the stopping rule. For example, if there have been 0/7 responses and patient #8 has been treated but not yet been fully evaluated at 4 months, then accrual will be suspended until that patient's outcome has been evaluated. If patient #8 has a response, then patients #9 - #20 may be treated. If patient #8 does not have a response, then accrual of

MRD patients will be terminated. The operating characteristics of this rule are as follows. Computations were carried out in Multc99.

Table 1. Operating characteristics of the rule for monitoring response in MRD patients.

True Pr(Response)	Prob(Stop early)	Achieved Sample Size Quartiles
.05	.82	8 8 20
.10	.54	8 20 25
.15	.32	8 25 25
.20	.18	25 25 25

Patients who have relapsed (REL). In this subgroup, response will be defined as disease remission at any time point within the first 6 cycles of therapy with SGI-110. Otherwise, the same design as that used in the MRD subgroup will be used.

7.2. High Risk Patients. This cohort will include high risk patients with one-year relapse incidence of 35%-45%. They will receive maintenance therapy with SGI for one year. A maximum of 40 patients will be enrolled. The primary endpoint for this cohort will be relapse-free survival (RFS) time. The Bayesian method of Thall et al will be used to monitor RFS time in this cohort (41). We denote the standard historical therapy by S and the experimental SGI-110 therapy by E. We assume that TS=time to disease progression or death in this cohort associated with standard therapy follows an exponential distribution with median mS and that TE=time to disease progression or death in these patients associated with the experimental SGI-110 therapy follows an exponential distribution with median mE. We denote the median RFS times for the standard and experimental therapies by mS and mE, respectively. Under a Bayesian model, both mS and mE are assumed to follow Inverse Gamma (a, b) priors, denoted IG(a, b). From historical data, Pr(TS > 12 months) = .35, which implies that the historical median RFS = 7.9 months in this group under the assumption of exponentially distributed RFS times. For priors, we assume that mS ~ IG (17.6, 131.2), which has mean = 7.9 months and variance = 4.0 months. We assume that mE ~ IG (3, 15.8), which has the same mean = 7.9 months but a much larger variance = 62.4. We will monitor possibly right-censored TE continuously through the trial and will terminate accrual to this cohort if at any time:

$$\Pr(mS < mE \mid \text{data}) < 0.07.$$

The accrual rate in this cohort is expected to be 2 patients per month. We will follow patients until all patients in the cohort have been followed for two years after transplant. We will enroll a maximum of 40 patients in this cohort.

Operating Characteristics. The operating characteristics of this stopping rule under the assumptions above were obtained by simulating the trial 2000 times each using the program One-Arm TTE v 3.0.6. These are summarized the table below.

Operating Characteristics of the Stopping Rule for Maintenance Patients

True Median RFS (months)	**True Pr (RFS > 12 months)**	**Pr (Stop Early)**	**Mean Sample Size**
4.4	.15	.827	21.8

6.0	.25	.339	32.5
7.9	.35	.103	37.3
10.4	.45	.036	39.0
13.9	.55	.009	39.7

Secondary outcomes. Secondary outcomes will include disease-free survival (DFS) time, relapse free survival (RFS), overall survival (OS) time, graft-versus-host disease, safety and duration of remission. Within each subgroup, these events will be tabulated and the distributions of RFS and OS time estimated using the method of Kaplan and Meier (42).

7.3 Cross-over. Patients treated on cohort #2 (patients with minimal residual disease while in morphological remission and cohort #3 (maintenance treatment cohort) will be allowed to receive higher doses of SGI-110 if they progress while on therapy with the study drug. Patients who are considered for cross-over to another study cohort due to progression of disease with an aim to receive higher doses of SGI-110 will be screened for the eligibility of that study cohort prior to initiation of higher doses of study drug. The subgroup of cross-over patients will be followed for evaluation of subsequent outcomes, such as response OS, starting from the date of cross-over.

8.0 Adverse Events and Reporting Requirements

8.1 Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product (IP) should be reported as an AE. If an overdose is associated with an AE, the overdose and AE should be reported as separate terms.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

Related AEs will be recorded by the Investigator from the time the subject signs informed consent to 30 days after the last dose of IP. The Investigator or physician designee is responsible for providing source documentation and assigning attribution for all AEs. Only related adverse events and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents.

Adverse events and protocol specific data will be entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol.

All SAEs must be reported to Astex Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

8.2 Evaluation of Adverse Events and Reporting to Astex Pharmaceuticals

A qualified Investigator will evaluate all AEs as to:

8.2.1 Seriousness

An SAE is any AE occurring at any dose that:

- Results in death
- Is life-threatening (ie, in the opinion of the investigator, the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay)
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g,, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.

- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

- A procedure that is planned (ie, planned prior to starting of treatment on study) must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- An elective treatment of a pre-existing condition unrelated to the studied indication.

- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

8.2.2 Severity / Intensity

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the currently active minor version of Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0).

AEs that are not defined in the CTCAE should be evaluated for severity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

- Grade 5 = Death - the event results in death

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as “serious” which is
based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject’s life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

8.2.3 Causality

The investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the AE to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	The temporal relationship of the AE to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

8.2.4 Duration

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

8.2.5 Action Taken

The investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

8.2.6 Outcome

All SAEs that have not resolved upon discontinuation of the subject’s participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

8.2.7 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not
a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

8.3 Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Astex Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent to 30 days after the last dose of IP), and those made known to the investigator at anytime thereafter that are suspected of being related to IP. Serious AEs occurring prior to treatment but after informed consent will be collected.

The SAE report should provide a detailed description of the SAE and include a summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Astex Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Astex Drug Safety.

8.4 Discontinuations

The following events are considered sufficient reasons for discontinuing a subject from study treatment:

- Disease progression and/or no response within the first 6 cycles of SGI-110 in addition to DLI as described in sections 4.2 and 6.0.
- Related and unexpected serious Adverse event(s)
- Development of grade III/IV acute GVHD or severe chronic GVHD
- Subject should receive the subsequent cycle within 70 days after the preceding cycle in cohort 2 and 3. If subject on cohort 2 and 3 cannot receive the subsequent cycle in 70 days, subject will be discontinued from study treatment.

- For patients on cohort 1, treatment cycles in the presence of disease (morphological relapse) can be delayed and subsequent cycles can be given at longer intervals at the discretion of treating physician and principal investigator.
- Withdrawal of consent
- Death
- Lost to follow up
- The investigator determines that the discontinuation of treatment is in the best interest of the patient.
- 60 days after the last cycle.

Although disease recurrence or progressive disease is considered a sufficient reason for discontinuing a subject from the study treatment, the investigator should consider continuing to treat the subject in attempt to hold the disease until the investigator has alternative therapies and considers the study treatment to be no longer beneficial to the subject, or the rapidity of change of disease state renders it unacceptable for further treatment in the judgment of the investigator.

The reason for discontinuation will be recorded in the eCRF and in the source document for all dosed subjects.

All subjects discontinued from study treatment for any reason will be followed further for GVHD status, progression to AML, and survival. Every attempt should be made to collect all data during the follow-up period unless subjects discontinue from the study.

8.5 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

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