Therapy Targeting the Interleukin-3 Receptor (IL3R) for Patients with Relapsed or Refractory and Elderly Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) with DT_{388}IL3 -SL-401 (IND# 11314): a Phase IB Clinical Trial

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I. Only patients with BPDCN will be screened for eligibility and, after eligibility is confirmed and informed consent obtained, pretreatment labs will be done and the patients will be admitted to University of Texas Southwestern Hospital and Clinics (see Section 4.1.2.1).

Patients will begin on prophylactic medications on day 1 continuing throughout the treatment period to prevent side effects including:

- 1 liter normal saline IV qd to maintain hydration for days of DT388IL3/SL-401 treatment.

Patients will be treated in-hospital, on a schedule of five daily doses with delays permitted between doses for a total maximum treatment period of ten days. No more than one dose may be given daily and no more than five total doses. One hour prior to drug administration, patients will receive:

- acetaminophen 325 mg po
- diphenhydramine 25 mg IV
- solumedrol 40 mg IV
- famotidine 20 mg IV

II. SL-401 will be administered into a free flowing normal saline IV over a period of approximately 15 minutes. Vital signs including blood pressure, pulse, temperature, respirations, and pulse oximetry will be measured post infusion, 30, 60, 180 minutes, and then every four hours thereafter. Strict Intake/Output and daily weights will be obtained during dosing days and the days following dosing. Blood draws (2cc) for pharmacokinetics (PK) will be done pretreatment and 5, 30, and 90 minutes post infusion on day 1 and identically for the fifth dose. Patients will be monitored closely for toxicities. Toxicities that were observed previously with DT_{388}IL3/SL-401 include fever, hypotension, dyspnea, hypoalbuminemia, weight gain, edema, and transaminasemia.

- Patients will have serum albumin monitored daily and will be given 25 grams of albumin each day the albumin is $\leq$3.0 gm/dL.
- Patients with >10% weight gain and no hypotension will receive furosemide IV as needed to prevent fluid overload.
- Patients with grade 3 respiratory compromise or grade 4 vascular leak toxicity will no longer receive the study drug and will be transferred (or admitted) to an ICU setting for monitoring and treatment at the physician's discretion.
- Chills associated with the administration of the study drug may be treated with meperidine 12.5-50 mg IV or morphine sulphate 1-2 mg IV as needed.
- Anaphylaxis and cytokine release syndrome associated with rash, fever, urticaria, bronchospasm, and angioedema will be treated with 100 mg IV methylprednisolone (or dexamethasone, or hydrocortisone at equipotent doses), diphenhydramine 25-50 mg IV. More severe symptoms will also be treated with 0.3cc epinephrine (1:1000) IV once only. Patients will be transferred to an ICU setting for monitoring.
- Patients with fever ≥ 100.5 degrees F will be cultured, given antibiotics and given acetaminophen 325mg po every 6 hours at the discretion of treating physician.
- Patients with mild to moderate dyspnea and hypoxia will receive

supplemental oxygen and furosemide as needed.
- Patients with hypotension (SBP < 90mmHg) will receive normal saline fluid bolus IV in volumes as needed to restore blood pressure.

III. The SL-401 dose is 12.5 µg/kg/day every day for five consecutive days. Delays between doses are permitted for recovery from toxicities as long as all doses are administered within 10 days. This 12.5 µg/kg/day dose corresponds to one dose level below the MTD determined for AML patients and is the recommended phase 2 dose level (RP2D). See Section 1.3 for details. If two patients experience drug-related dose limiting toxicity, the MTD for BPDCN patients has been exceeded, enrollment to that dose will stop, and the next lower dose from the AML phase 1 study--10µg/kg may be tested on additional patients after consultation with the DSMC, IRB and FDA. If 2 patients in the lower dose cohort experience dose-limiting toxicity (drug related grade 3 or 4 with the exceptions described 4.1.10), study accrual will be halted.

IV. Dose-limiting toxicity (DLT) is defined as any drug-related grade 4 hematologic toxicity (unrelated to persistent leukemia) lasting > 28 days after the last day of therapy or non-hematologic toxicity of grade 3 toxicity except for transient (≤2weeks) asymptomatic transaminase or CPK elevations.

V. Additional BPDCN patients will be treated until a total of 11 patients have been treated at the RP2D or BPDCN MTD—the lowest between these. Response will be determined based on previous recommendations for response criteria for BPDCN [1, 2].

VI. Correlative studies include the evaluation of response and toxicity in relation to pretreatment marrow blast index (product of percent blasts x marrow cellularity), presence of skin disease, presence of nodal disease or organomegaly by PET/CTscan, presence of circulating blasts, age, gender, prior therapies, and blast surface density of CD123.

1.0 Background of BPDCN and Rationale

BPDCN is a rare hematologic malignancy of plasmacytoid dendritic cells with an incidence of approximately 50 patients/y in the United States. The median age at diagnosis is 65 years and most patients are male. Patients may present with involvement of skin, marrow, and blood, and, less frequently, node, liver and spleen. Diagnosis entails immunohistochemical evidence of malignant CD4+CD56+CD123+TCL1+CD303+ blasts [3]. Treatment consists of combination chemotherapy and allogeneic bone marrow transplantation [1, 4]. Median survival is 12-18 months. While preclinical data suggests anti-BPDCN activity of lenalidomide [5], no clinical trials have been reported with lenalidomide for relapsed BPDCN. Patients frequently die from leukemic progression.

1.1 Fusion Protein Therapy of BPDCN

One set of agents designed for extreme potency is fusion proteins consisting of protein synthesis inactivating peptide toxins fused to leukemia cell selective ligands. Our laboratory has used diphtheria toxin (DT), a 535 amino acid residue protein with three domains--a catalytic domain (amino acid residues 1-186) connected by a arginine-rich disulfide loop to a translocation domain (amino acids 187-388) followed by a cell binding domain (amino acids 389-535) [6]. DT binds to a heparin-binding epidermal growth factor precursor on the cell surface and undergoes receptor-mediated endocytosis [7]. In the early endosomes, DT is cleaved by furin, and, in the acidic environment, the translocation domain helices insert into the vesicle membrane. Cytosolic beta-

COP, Hsp90 and thioredoxin reductase facilitate the escape of the DT A fragment containing the catalytic domain to the cytosol [8]. In the cytosol, the A fragment ADP-ribosylates elongation factor 2 leading to inhibition of protein synthesis and programmed cell death or necrosis [9].

We constructed the fusion protein DT_{388}GMCSF composed of the catalytic and translocation domains of DT fused via a Met-His linker to human granulocyte-macrophage colony-stimulating factor [10]. The fusion protein was selectively toxic to AML cell lines and patient progenitors [11, 12] and showed *in vivo* anti-leukemic efficacy in SCID mice bearing human leukemias [13]. A clinical batch of drug was prepared and 38 patients with relapsed or refractory AML were treated with up to five daily bolus infusions [14]. Remissions were observed in four patients lasting up to one year, but liver injury, presumably due to hepatic Kupffer cell expression of the GM-CSF receptor, was observed which prevented dose escalation. Because of the toxicity of DT_{388}GMCSF, our laboratory sought to design and produce an alternative fusion protein that was not only more potent but which, by virtue of targeting a more tumor-specific surface receptor, was more selective for malignant cells and thus less toxic. The interleukin-3 receptor (IL3R), a target with a more tumor-specific expression pattern, was chosen for these reasons. Moreover, IL3R is an additionally attractive target because it is over-expressed on some progenitor cells of myeloid malignancies [15, 16].

Interleukin-3 (IL3) is a cytokine, which supports the proliferation and terminal differentiation of certain multi-potential and committed myeloid and lymphoid progenitors. The IL3R is composed of an α and β subunit, and binding of IL3 to the receptor causes rapid internalization of the ligand-receptor complex [17]. IL3R are overexpressed on human myeloid leukemic stem cells and progenitors but low-absent on normal human hematopoietic stem cells, and leukemic cells proliferate in response to exogenous IL3 [18]. High affinity IL3R are absent from most normal tissues [19]. Low affinity IL3R have been reported on human mast cells, endothelium, testes and brain, but it is not known whether these non-hematopoietic receptors are able to internalize ligand [20 - 23]. Rhesus monkeys have receptors, which can bind and physiologically respond to human IL3 [24]. Two groups prepared DT fusion proteins with murine IL3 [25, 26]. In both cases, selective cytotoxicity to murine malignant myeloid cells was observed. A fraction of normal murine stem cells was spared. Anti-leukemic efficacy was observed in a murine leukemia model. Because of the broad range of expression of IL3R among myeloid leukemias, its absence from most normal tissues including normal human hematopoietic stem cells, its rapid internalization on cross-linking, the availability of a relevant animal model for safety testing, and the encouraging results with a murine receptor targeted DT fusion protein, we chose IL3 for construction of the next generation fusion protein.

1.2 Preclinical Information on DT_{388}IL3

Constructions. Plasmids encoding four different DT_{388}IL3 molecules were made, and recombinant proteins were produced in *E. coli* [27]. The molecules included DT_{388}-Met-His-human IL3, DT_{388}-Met-His-$(Gly_4\text{-}Ser)_2$-human IL3, DT_{388}-Met-His-humanIL3-Leu-Glu-$(His)_6$, and Met-Gly-$(Ser)_2$-$(His)_6$-$(Ser)_2$-Gly-Leu-Val-Pro-Arg-Gly-Ser-His-Met-Ala-Ser-Met-DT_{388}- Met-His-human IL3. The DT_{388}-Met-His-human IL3 or SL-401 gave the best yields, purity, IL3R affinity and potency.

Selective cytotoxicity to cell lines. Inhibition of thymidine incorporation, inhibition of colony formation, and apoptosis induction were measured after SL-401 incubation with eight human AML cell lines [28]. Four of eight AML cell lines were sensitive with IC_{50}s of 1 to 50pM. SL-401 sensitivity correlated with the number of high affinity IL3R ($p = 0.03$).

Efficacy for leukemic cell killing. Inhibition of human AML colony-forming cells (AML-CFC) with SL-401 exposure was measured in three studies [29 - 31]. Greater than one log cell kill was observed in 3/9, 3/7 and 9/25 samples, respectively. In the last study, a correlation between log cell kill and blast high affinity IL3R density was found ($p = 0.004$). In the second study, inhibition of earlier

leukemic stem cells (long-term culture-initiating cells, suspension culture-initiating cells, and NOD/SCID mice engrafting cells) was also observed in 3/7 samples. In each of these three samples, the surviving treated human cells lacked the leukemic cytogenetic abnormality.

Safety on normal stem cells. Normal marrow progenitors were incubated with SL-401 and assayed for colony growth and NOD/SCID mice repopulating frequency [32]. There was a 60-80% reduction in colony-forming cells but no inhibition of long-term culture-initiating cells, suspension culture-initiating cells, or NOD/SCID mice engrafting cells.

Safety and efficacy in rodent models. Six week old C57BL/6 female mice tolerated six every other day intraperitoneal infusions of 375 μg/kg SL-401 with a DLT of renal tubular necrosis [33]. We developed an *in vivo* model of differentiated human AML by retroviral infection of the cytokine-dependent human AML cell line TF-1 with the v-Src oncogene [34]. When injected either intravenously into 300 cGy irradiated SCID mice, animals formed multiple granulocytic sarcomas involving the adrenals, kidneys, lymph nodes and other organs. Leukemic mice treated with 100 μg/kg with five daily intraperitoneal doses of DT_{388}IL3 had a significant prolongation in disease-free survival (>120 days versus 37 days, $p < 0.001$) and only 5/49 (10%) of treated leukemic mice died with leukemia [35]. In a separate study, NOD/SCID mice engrafted with six different human AML samples treated with SL-401 had significant reductions in AML engraftment at twelve weeks for four of six samples and no evidence of residual leukemia for two of the AML samples [36].

Safety in monkeys. Eight cynomolgus monkeys received up to six every other day intravenous infusions of SL-401 40μg/kg (n = 2), 60 μg/kg (n = 2), or 100μg/kg (n = 4) [37, 38]. After one week, all monkeys were necropsied. One female monkey given 100μg/kg drug died with vasculitis. The remaining seven monkeys showed either no symptoms or mild to moderate transient malaise and anorexia. There were no reproducible blood test abnormalities or organ damage by histopathology. The drug half-life was 30 minutes, and immune responses were minimal. The SL-401 MTD was fifteen-fold higher than the DT_{388}GMCSF MTD. No significant myelosuppression or liver injury was seen.

Lack of toxicity to macrophages. DT_{388}mGMCSF but not DT_{388}mIL3 produces elevations of serum transaminases in rodents [39]. In tissue culture, DT_{388}mGMCSF but not DT_{388}mIL3 damages liver macrophages. Cultured human monocytes released tumor necrosis factor-alpha in response to DT_{388}GMCSF but not SL-401 [40]. These observations along with the findings in monkeys suggest SL-401 may produce less liver toxicity than DT_{388}GMCSF in patients.

Vascular leak syndrome (VLS) toxicity of fusion proteins. One to two weeks after systemically administered peptide toxins and cytokines, vascular damage may occur with hypoalbuminemia, hypotension, edema, dyspnea, weight gain and, rarely, hypoxemia. Tripeptide disintegrin motifs may bind to receptors on endothelial cells triggering vascular permeability or apoptosis [41]. There are three disintegrin motifs at amino acid residues 7-9, 29-31 and 208-210 of SL-401 that may produce VLS similar to DT_{388}GMCSF and denileukin diftitox [42].

CGMP lots approved. Recombinant protein was produced in *E. coli* [33]. Inclusion bodies were washed, denatured and refolded, and protein dialyzed and purified by column chromatography. Seventy-five 3-L bacterial culture preparations were made and pooled for the AT-1 batch (568 mL) and twenty-four 3-L bacterial culture preparations made and pooled for the AT-2 batch (169 mL). Final material was filter sterilized, aseptically vialed and labeled in 1 mL aliquots, stored at -75ºC or below, and characterized by Coomassie Plus protein assay, Coomassie-stained SDS-PAGE, limulus amebocyte lysate endotoxin assay, human AML TF/H-ras cell cytotoxicity assay, sterility, tandem mass spectroscopy, IL3 receptor binding affinity, ADP ribosylation activity, inhibition of normal CFU-GM, disulfide bone analysis, immunoblots, peptide mapping, stability, HPLC TSK3000, N-terminal sequencing, *E. coli* DNA contamination, C57BL/6 mouse toxicity, cynomolgus monkey toxicity, and immunohistochemistry. FDA approval (IND #11314) for clinical testing was obtained on 11/3/03.

Pre-clinical studies in BPDCN. Recently, SL-401 was incubated *in vitro* with BPDCN cell lines and fresh BPDCN blasts from six patients and femtomolar cytotoxicity observed both by MTT assay and annexin V staining [43].

1.3 Clinical information on SL-401

A Phase I dose escalation study was undertaken in 74 patients with relapsed or refractory adult AML (n = 56), de novo poor risk elderly AML (n = 11), or high-risk myelodysplastic syndrome (MDS) (n=7). Thirty-three AML patients were ≥2nd salvage. Thirty-six percent of the patient's had unfavorable cytogenetics, 59% had intermediate cytogenetics, and 0% had favorable cytogenetics. The cytogenetics for 5% of the patients were not determined. The median patient age was 66 years (range, 24-84). Patients received SL-401 via a 15 minute intravenous infusion in one of two dosing regimens for one cycle to determine the MTD and to evaluate clinical activity. In the first regimen, Regimen A, 45 patients received doses ranging from 4 to 12.5 mcg/kg every other day for up to six doses [44]. In the second regimen, Regimen B, 29 patients received doses ranging from 7.1 to 22.1 mcg/kg daily for up to 5 doses [45]. SL-401 was well-tolerated at clinically active doses. Adverse events (AEs) that were observed during the trial included grade 1-2 hypoalbuminemia (62%) that was manageable and not dose-limiting. Other less common grade 1-2 AEs included fever and chills, which were largely infusion-related. Grade 3 or greater AEs included transaminase elevations (21%), which were mostly transient, and which was the DLT at 22.1 mcg/kg daily for five days. The MTD for Regimen B was established at 16.6 mcg/kg daily for five doses. An MTD was not defined for the Regimen A schedule. Notably, there was no treatment-related delayed recovery of the bone marrow. This is consistent with the known over-expression of the drug's target, IL-3R, on leukemia versus normal hematopoietic stem cells. Absolute neutrophil count and hemoglobin remained stable, and near or above baseline pre-treatment levels, throughout therapy and up to day 30 post-infusion. Mean platelet counts were 58,000/uL pre-treatment, 30,000/uL at Day 15, and back to baseline by Day 30. Overall, two complete remissions (CRs), 4 partial responses (PRs), and 14 minor responses (MRs) including 4 with ≥50% reduction in blasts were observed during the trial. In addition, anti-tumor activity, defined as blast reductions or disease stabilization, was seen in 46% of patients with relapsed or refractory AML, 55% of poor risk elderly AML, and 43% of high risk MDS patients. Durable CRs were induced in two patients with chemorefractory AML. One patient, who sustained a CR of greater than 15 months duration, had a previous history of refractory AML, including two stem cell transplants, and had relapsed for a third time prior to entry onto this study. The second patient had a sustained CR of 8 months duration, after failing standard AML induction chemotherapy. This is consistent with the dual mechanism of action of SL-401 targeting both blasts and leukemia stem cells. In addition, the median survival of ≥2nd salvage AML patients was 3.2 months (95% CI: 2.0, 8.4) and the 12 months overall survival was 22% (95% CI: 5.1, 45.7), which is favorable compared with historical 12-months survival of 2-8%. Also of note, SL-401 demonstrated a clinical anti-cancer stem cell (CSC) effect as evidenced by a decrease in CSC activity in patient bone marrows (n=3), as determined by an *ex vivo* colony formation assay pre- and post-SL-401 treatment. The results from these 74 patients have been published [45].

Recently, three BPDCN patients received 3-5 doses of SL-401 over 5-10 days at 12.5μg/kg over 15 minute infusions. Toxicities were limited to transient transaminasemia, fever, chills, hypoalbuminemia, dyspnea and weight gain. Drug half-life was 65 minutes and anti-drug antibodies formed after two weeks. All three patients achieved complete remissions lasting 1, 5, and 7months.

2.0 Objectives

2.1 Evaluate response rate

2.2 Assess the tolerability of the RP2D—five daily dose of 12.5μg/kg as 15 min bolus IV infusion with delays permitted up to 10 days in BPDCN patients.

2.3 Define any DLTs of this SL-401 regimen in these patients.

2.4 Measure the pharmacokinetics and immune responses associated with this SL-401 regimen.

2.5 Correlate response with patient disease burden and IL3 receptor density.

3.0 Patient Selection Criteria

3.1 Eligibility

3.1.1 All patients must be informed about the study and signed informed consent.

3.1.2 All patients must have BPDCN diagnosed by morphologic, histochemical and cell surface marker criteria [3].

3.1.3 All patients must have failed or be intolerant of chemotherapy and allogeneic stem cell transplantation.

3.1.4 Patients must have a performance status of ≤ 2 on the ECOG scale

3.1.5 Patients must have bilirubin ≤1.5 mg/dl, transaminases <2.5x upper limit of normal, albumin ≥3gm/dl, creatinine ≤1.5mg/dl, and adequate cardiac reserve (EF≥50%).

3.1.6 Must give written informed consent.

3.1.7 Must be willing to be treated at the University of Texas Southwestern Hospital and clinics.

3.1.8 Females and males must be willing to use an approved form of birth control while on this study and for 2 weeks after completion.

3.1.9 Age ≥ 18 years.

3.2 Ineligibility

3.2.1 Failure to meet any of the criteria set forth in Section 3.1.

3.2.2 Inability to give informed consent because of psychiatric problems, or complicated medical problems.

3.2.3 Serious concurrent medical problems, uncontrolled infections, DIC or pregnancy.

3.2.4 Active CNS leukemia.

3.2.5 Patients who have had a myocardial infarction within the past six months.

3.2.6 Pregnant or nursing women will be excluded from study.

3.2.7 Patients with allergies to diphtheria toxin will be excluded.

3.2.8 Patients requiring oxygen will be excluded from the study.

3.2.9 History of congestive heart failure.

4.0 Treatment Plan

4.1 Study Design

Prior to Therapy

4.1.1 Patient sera will be collected and assayed for anti-SL-401 EIA antibodies as described [46].

4.1.2 Prior to commencing treatment on any day patient must have a serum creatinine $\leq$1.5mg/dL to continue drug.

4.1.3 Patients are admitted to University of Texas Southwestern Hospital and Clinics and given normal saline 1 liter IV every day of treatment.

- normal saline 1L IV qd

Patients will receive treatment for a maximum of five doses over 10 days at a maximum of once daily; if there is no drug-related grade 3 non-hematologic toxicity, albumin is $\geq$2.7 gm/dL and serum creatinine is $\leq$1.5mg/dL. Patients will receive 1h prior to each SL-401 treatment:

- acetaminophen 325 mg po
- diphenhydramine 25 mg IV
- solumedrol 40 mg IV
- famotidine 20 mg IV

The prophylactic regimen was chosen based on the results of the initial phase I studies of SL-401.

Therapy

4.1.4 Patients will be treated with a maximum of five doses of approximately 15min IV infusions of SL-401 over a ten day period at a maximum of once daily. The second through fifth doses for each patient will only be given if repeat serum creatinine is $\leq$1.5 mg/dL,albumin is $\geq$2.7 gm/dL and there is no drug-related

grade ≥3 non-hematologic toxicity prior to each treatment. If albumin is <2.7 gm/dL, treatment will be held for the day, albumin will be replaced to ≥2.7 gm/dL, and treatment can be resumed the following day. All 5 doses must be completed within 10 days.

4.1.5 If two patients experience drug-related dose limiting toxicity, the MTD has been exceeded, enrollment at the 12.5μg/kg dose will stop, and patients will be treated at the next lower dose 10μg/kg. If 2 patients experience DLT at this lower dose level, the study will be halted.

4.1.6 A total of eleven patients will be treated.

4.1.7 Toxicity will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Drug-related DLT is defined for this protocol as any nonhematologic drug-related toxicity of grade 3 except transient (≤2 weeks) asymptomatic transaminase or CPK elevations or any grade 4 drug-related hematologic toxicity (unrelated to leukemia) lasting > 4 weeks after the last dose of SL-401.

4.1.8 All patients entered on this phase I study will be evaluated for response as outlined in section 7.0. All patients will have pharmacologic and immunologic studies performed as outlined in section 8.0.

4.1.9 Patients may receive additional treatments with DTIL3 if they have a low antibody titer of less than 16ug/ML and partial or complete response to first cycle. Patients have had no toxicities at any anti-DTIL3 level observed pre-treatment. The range has been 0-60ug/ML. Antibody levels less than 10ug/mL do not affect DTIL3 pharmacokinetics and hence patients with less than 10ug/mL are most likely to respond.

4.2 Treatment Schedule and Duration SL-401 Fusion Protein Therapy

4.2.1 Patients are admitted to UT Southwestern Medical Center Hospital and Clinics and given prophylactic medications to prevent side effects. Pretreatment medications include acetaminophen 325 mg po, diphenhydramine 25 mg IV, solumedrol 40 mg IV, and famotidine 20 mg IV on treatment days one hour before treatment. Normal saline will be given at 100 cc per hour while the patient is hospitalized for treatment. This may be modified at the physician's discretion, but at least one liter of normal saline will be given each of the treatment days. Vital signs will be obtained pre-treatment including temperature, respirations, BP, Pulse, and pulse oximetry.

4.2.2 Starting on first treatment day and repeated on each treatment day after premedication and pre-treatment lab draws and vital signs measurements, SL-401 fusion protein will be administered into a free flowing IV of normal saline over a period of approximately 15 minutes. On treatment days, vital signs will be measured post infusion at 30 (+/- 5 minutes), 60 (+/- 10 minutes), and 180 (+/- 10 minutes) minutes, and then q4h (+/- 10 minutes). Vital signs include BP, pulse, temperature, respirations and pulse oximetry. Strict input and output (I/O) and daily weights will be obtained on treatment days. Patients are required to have a Temperature <100.5^{o} F, Pulse <130 and >40, and Systolic BP<160 and >80 mmHg prior to therapy.

4.2.3 Chills associated with study drug administration may be treated with meperidine 12.5-50 mg IV or morphine sulphate 1-2 mg IV. Anaphylaxis and hypersensitivity reactions associated with rash, fever, urticaria, bronchospasm, and angioedema will be treated with 100 mg IV methylprednisolone (may substitute for dexamethasone, or hydrocortisone at equipotent doses), 25-50 mg IV diphenhydramine. More severe symptoms will also be treated with 0.3 cc epinephrine (1:1000) IV once. Patients will be transferred to an ICU setting for monitoring with Pulse>140 or <40, SBP >160 or <80 mmHg, or oxygen saturation <90% or any physical signs or symptoms of anaphylaxis and hypersensitivity at the physician's discretion. Patients with anaphylactoid reactions or hypersensitivity reactions will be treated for symptoms receive no further SL-401 and be taken off study.

4.2.4 Symptomatic hypotension will be treated with a bolus of 500 cc normal saline and a hold on further drug infusion until resolution. If the BP fails to improve with two 500 cc bolus saline infusions, further standard measures to correct the BP will be undertaken and the drug will be withheld on that day. If low BP, without further drug treatment through the next day, no further drug will be given to that patient for that course.

4.2.5 Vascular leak syndrome is associated with vascular endothelial injury related to fusion protein administration and may occur 3-8 days after initiation of treatment. Patients may note symptoms of hypotension, weight gain, edema, nausea, and anorexia, shortness of breath and, at times, confusion and muscle injury. Exam findings may include hypoalbuminemia, reductions in blood oxygen saturation, and chest X-ray pulmonary edema. Patients with hypotension will receive 500cc normal saline boluses. Patients will have serum albumin measurements daily until completion of the drug administration and will receive 25gm albumin IV each day the serum albumin is <3 gm/dL. Patients with >10% weight gain and no hypotension will receive furosemide as clinically indicated. Patients with grade 3 respiratory compromise or grade 4 vascular leak toxicity, due to the study drug, will no longer receive the study drug and will be transferred to an ICU setting for monitoring and treatment. Reversibility of low blood pressure or hypoxemia with fluids and diuretic, responding within 24 hours will not constitute grade 3 vascular leak syndrome.

4.2.6 Peripheral blood counts will be monitored daily during treatment period and then the following day. Bone marrow aspiration and biopsy will be done on days 15 (+/- 1 day) and 30 (+/- 1 day). Serum chemistries including transaminases, CPK, calcium, creatinine, alkaline phosphatase, bilirubin will be done daily on days 1-6. CMP will be repeated on days 15 (+/- 1 day) and 30 (+/- 1 day). Urinalysis will be done weekly and on days 15 (+/- 1 day), and 30 (+/- 1 day). Any grade 3 or greater laboratory abnormalities will be followed with increased frequency as appropriate until resolution of toxicity. Thrombocytopenia and anemia will be treated with blood products as clinically indicated. Cryoprecipitate may be used to replace fibrinogen for levels <100 mg/dL as cryoprecipitate does not contain significant anti-DT_{388}IL3 antibodies. Elevated prothrombin times (INR >2.0) in the absence of other abnormalities consistent with DIC will be treated after the end of fusion protein infusions (day 6) with fresh frozen plasma one unit daily for one week or until INR <2.0. If the prothrombin time is prolonged to INR >2.5, the patient will be treated with fresh frozen plasma one unit daily and continued

on study. Vitamin K 5mg IV every day may also be used for elevated prothrombin time.

4.2.7 Patients with partial remission (PR) or complete remission (CR) at day 30 (+/- 1 day) marrow and blood sampling, skin exam, and PET/CT scan will have repeat bone marrow exam, skin exam and PET/CTscan at day 60 (+/- 1 day) to assess duration of response.

4.2.8 Patients will be withdrawn from the study if they show obvious evidence of progressive disease while on therapy prior to day 15 (+/- 1 day) marrow and blood analysis. Non-responding patients or patients with progression may be further treated with other investigational or standard chemotherapy agents.

4.2.9 Patients may be re-treated if there is disease progression more than 30 days after their initial treatment.

4.3 CNS Leukemia

Documented CNS leukemia while on study will necessitate removal from study and treatment at the discretion of the patient's principal physician.

4.4 Concomitant Treatment

4.4.1 Patients should receive full supportive care including transfusions of blood and blood products, antibiotics, antiemetics, etc, when appropriate. Antiemetics should not include corticosteroids. Any hematopoietic growth factors (e.g., erythropoietin, interleukin-11, G-CSF and GM-CSF) are not allowed. Patients are not allowed intravenous immunoglobulins while on the study.

4.4.2 Treatment with other anti-neoplastic drugs after the start of SL-401 therapy will result in the patient's removal from study.

4.4.3 Radiation therapy may not be administered while the patient is on this study.

5.0
Study Parameters

5.1 Study Parameter Table (see section 4.2)

	Screening[a]	Days1-10[l]	Day 15 (+/- 1 day)	Day 30 (+/- 1 day)	Response Follow-up[b m]
History and Physical[c]	X	X	X	X	X
Bone marrow Aspirate & Bx[d]	X			X	X
Toxicity Notation	X	X	X	X	X
CBC with Differential	X	X	X	X	X
DIC Screen and CPK	X	X			X [k]
Urinalysis	X	X [e]	X		
CMP[f], LDH, uric acid	X	X	X	X	X
Chest x-ray (PA & lateral)	X				
EKG,EF	X			X[g]	
Skin exam/photographs/bx[j]	X		X[j]	X[j]	X[j]
PET/CTscanj	X			X[j]	X[j]
Pregnancy test (β–HCG)[h]	X				
PK & Immune Studies [i]		X	X	X	
LP [j]	X				

[a]Screening tests should be performed within 28 days of the start of treatment. CBC with differential, CMP, DIC screen and CPK should be performed within 1 week of the start of treatment
[b]See section 5.4.
[c]See section 5.2.
[d]See section 5.3.
[e]Urinalysis is only done once per week and at days 15 and 30, or as clinically indicated.
[f]CMP including sodium, potassium, chloride, CO2, BUN, glucose, creatinine, calcium, total protein, albumin, total bilirubin, SGOT, SGPT and alk phosphatase.
[g]EF repeated at one month.

[h]Females of reproductive potential
[i]See section 5.5. Note PK draws on first and last treatment day. Immune draws on days 1, 15, and 30.
[j]As clinically indicated.
[k]CPK only
[l]Only on treatment days
**. Scheduled procedures, labs and treatment may be modified by +/- 1 day due to the presence of weekends, vacations, or clinically necessary procedures.

5.2 Physical Examinations

5.2.1 Screening

A detailed history and physical examination must be performed including weight, height and body surface area. Records of prior therapy with duration, dates and performance status must be recorded. A detailed neurologic exam and fundoscopic exam will be performed as clinically indicated.

5.2.2 Treatment Period

A detailed history and physical examination must be performed including weight. We will monitor for altered sensorium, headaches or focal neurological findings and complete a detailed neurologic and fundoscopic exam as clinically indicated. Patients will be followed by nephrology during treatment days if indicated.*

5.2.3 Photographs will be taken to document lesion changes and response to treatment. *

5.3 Bone marrow aspirate and biopsy during off-treatment follow-up must be every three months (+/- 2 weeks) for 1 year, then at least semiannually (+/- 3 weeks) for years 2 and follow-up for 5 years and study will be completed if there was initial marrow involvement and a remission is obtained. Bone marrow aspirate and biopsy must have differential and estimate of cellularity. A bone marrow aspirate for immunophenotyping should be done with marker analysis for CD4, CD56, and CD123 costained populations. Bone marrow cytogenetics must be performed. Cytogenetics, histochemistry, and FAB classification need only be performed on the initial pretreatment aspirate and biopsy. Follow-up bone marrows must have peripheral blood CBC and Differentials.

5.4 Off-treatment follow-up for patients obtaining remissions will be monthly (+/- 1 day) for the first 3 months, then every 3 months for 1 year, then every 6 months for years 2 and follow-up for 5 years and study will be completed with CBC, differential and platelet counts, and CMP, CPK, LDH, bone marrow aspirate and biopsy every 3 months (+/- 2 weeks), if marrow positive initially for patients with a remission from therapy. Again, bone marrow aspirates should assess CD4+CD56+CD123+ populations. Off treatment follow-up for progressing or non-responding patients will be for survival and patients will be contacted by phone. Additional therapy data may be collected from their primary care physician.*

*Procedures, Physical Exam, labs, photographs (as clinically indicated), bone marrow aspirate, biopsy, and PET/CT scan can be done where the patients reside and sent to the Research Coordinator at UT Southwestern Medical Center.

5.5 Correlative Studies

5.5.1 Circulating concentrations of biologically active SL-401 fusion protein in the blood sent to Scott & White Cancer Research Institute.

Measurement of the half-life of SL-401 in the blood in patients will permit correlation of drug levels and leukemia cell exposure (time x concentration) with clinical toxicities and response. Further, different patient leukemia burdens may influence drug pharmacodynamics.

2 ml venous blood samples (red tops) will be drawn at the times shown below. Blood will be allowed to clot 30 minutes at room temperature and then centrifuged 2,000g x 15 minutes, and serum collected and frozen at -75°C or below until assayed for SL-401 bioactive concentration. Label tube with study number, patient's initials, patient ID number, date, and time of draw. Store blood samples at -75°C or below until delivered. Please deliver samples to Jung Hee Woo, PhD, Cancer Research Institute, 5701 South Airport Road, Temple, Texas 76502.

Blood samples (red tops) will be obtained pretreatment and at 5, 30, and 90 minutes post-infusion on the first treatment day and identically on the last treatment day.

Serum samples collected pretreatment and at 5, 30, and 90 minutes post-infusion on the first and last treatment day infusions will be collected and stored at -75°C or below until assayed. Ten microliters of normal human serum will be mixed with 1 μL of SL-401 and 89 μL of RPMI 1640 (BioWhittaker, Walkersville, MD) plus 10% fetal bovine serum (FBS, Irvine Scientific, Irvine, CA) to yield a final concentration of 19 μg/mL SL-401. Thirty microliters of this mixture will be combined with 60 μL of RPMI1640/10% FBS, with 10 further dilutions (1:3) prepared sequentially for the standard curve. Similarly, for the rest of the samples, 10 μL of sample patient serum will be mixed with 90 μL of RPMI1640/10% FBS, and again one to three dilutions were prepared sequentially by adding 30 μL of each dilution to 60 μL of RPMI1640/10% FBS. Fifty microliters of medium containing the patient serum samples or standards will be added to 100 μL of medium with 5000 TF/H-ras cells in flat-bottom sterile 96-well Costar plates and incubated at 37°C/5% CO_2 for 48 h [44]. Fifty microliters of medium containing 0.5 μCi [^{3}H]thymidine (DuPont NEN, Boston, MA) will then be added to each well and incubation continued at 37°C/5% CO_2 for an additional 16 h. Cells will then be harvested on a cell harvester (Skatron Instruments, Sterling, VA) to glass fiber mats, and the [^{3}H]thymidine counted in a Wallac Betaplate Reader gated for ^{3}H. The dilution of patient serum sample yielding a 50% reduction in thymidine incorporation (IC_{50}) will be compared to the standard curve to estimate the SL-401 concentration. All assays will be performed in duplicate.

5.5.2 Circulating anti-fusion protein Ig concentration sent to University of Texas Southwestern Medical Center

2 ml venous blood sample (red tops) will be collected and these are different than those obtained in 5.5.1 and sera harvested identically to 5.5.1 and stored at -75°C or below until assayed. Label tube with study number, patient initials, patient ID number, date, and time of draw. Store blood samples at -75°C or below until delivered. Please deliver samples to Jung Hee Woo, PhD, Cancer Research Institute, 5701 South Airport Road, Temple, Texas 76502.

Blood samples will be obtained pretreatment on day 1 and on days 15 and 30. Thus, only three samples collected during the course for the immune measurements.

5.5.3 Patient marrow BPDCN blast CD123 quantitation

Pretreatment and day 30 bone marrow aspirates will undergo CD123 quantitation on BPDCN cell population using clinical laboratory reagents and measurements.

6.0 Treatment Modifications

6.1 Reasons for Study Discontinuation

6.1.1 Progressive disease

6.1.2 Death

6.1.3 Unacceptable study drug toxicity

6.1.4 Patient refusal to continue on protocol

6.1.5 Physician's judgment that discontinuation is in the best interest of the patient

6.1.6 Sponsor's decision to discontinue protocol for technical reasons

6.2 Treatment Modification--Therapy Courses

6.2.1 Hematologic—None

6.2.2 Non-hematologic--Occurrence of any DLT (Section 4.1.7) or drug-related grade 3 non-hematologic toxicity except for transient (≤ 2 weeks) asymptomatic transaminase or CPK elevations, during the course of therapy will result in immediate discontinuation of the infusion and observation for resolution of the toxicity. Additionally, if albumin is <2.7 gm/dL, treatment will be held for the day, albumin will be replaced to ≥2.7 gm/dL, and treatment can be resumed the following day. In order to receive treatment on any given day, the patient's creatinine must be ≤1.5mg/dL. Treatment all 5 doses must be completed within 10 days.

6.3 Response Evaluation Criteria

The BPDCN response criteria are based on published recommendations [1, 2] as shown below:

6.3.1 Complete Response (CR)
- -Normal WBC, Platelets with absent blasts in peripheral bood or Marrow
- -No evidence nodal involvement or liver/spleen involvement by CT Scans or PET/CT scan
- -No skin involvement by exam and biopsy where necessary.

6.3.2 Partial Remission (PR):
- - Decrease of 50% of more in marrow blasts
- - Decrease in nodes/liver/spleen size as per RECIST1.1 criteria.
- - Decrease of 50% or more in skin lesions.

6.3.3 Stable Disease:
- -Failure to achieve at least PR, no evidence progression for 2 months

6.3.4 Failure:
- -Death during treatment or disease progression characterized by:
- -increase in the percentage bone marrow blasts

-increase in skin or node or liver/spleen size.

6.4 End Point Variables

-DLT (defined in Section 4.1.7)
-Toxicity profile (described in Section 4.1.7 (defined in Section 4.1.5)
-Clinical response rate (as measured in Section 7.0)
-Duration of response--defined as time of first response to time of progression.
-Anti-SL-401 antibodies at day 1, 15, 30 (see Section 8.5)
-Serum SL-401 levels and half-life (see Section 8.5)
-Pretreatment marrow blast index and BPDCN blast CD123 density (section 8.5)

6.3 Toxicity Criteria

Toxicity will be determined using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for Toxicity and Adverse Event reporting. A copy of the CTCAE version 4.0 can be downloaded from CTEP home page (http://ctep.info.nih.gov).

6.4 Toxicity Reporting

6.4.1 Notify PI, Dr. Arthur Frankel (214) 648-1579 immediately by telephone of dose-limiting toxicity as defined by protocol and document in the patient's medical records and protocol forms that the chairman was notified.

6.4.2 Any pronounced, unusual or unexpected toxicity should be reported immediately to the PI, Dr. Arthur Frankel (214) 648-1579. The PI must obtain a detailed clinical description of the toxicity and report it to the IRB and decide whether it should be reported to the FDA . Other study participants will be notified. If the toxicity is reportable, the Study Chairperson will be responsible for notifying the FDA as per Federal Register §312.32 IND safety reports. In particular, (1) Written reports. The PI/Study Chairperson/Sponsor shall notify FDA in a written IND safety report of any adverse experiences associated with use of the drug that is serious and unexpected. Such notification shall be made as soon as possible and no later than 10 working days after the Sponsor/Study Chairperson's initial receipt of the information. The written notification to the FDA will be transmitted to the FDA Division of the Center for Drugs and Biologics. (2) Telephone reports. The Sponsor shall also notify FDA by telephone of any unexpected, fatal or life-threatening experience associated with use of the drug in the clinical study conducted under the IND no later than 3 working days after receipt of the information and will be transmitted to the FDA Division of the Center for Drugs and Biologics, which has responsibility for review of the IND.

6.4.3 Any questions regarding this protocol should be directed to the Study Chairperson/PI:

Arthur E. Frankel, MD
UT Southwestern Medical Center
Dallas, TX
(214) 648-1579

7.0 ADVERSE EVENTS

7.1 Experimental Therapy
For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2.1 Definition

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, that occurs during the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

7.2.2 Unanticipated Problems:

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ***each*** of the following criteria:

- unexpected; ***and***
- related *or possibly related* to participation in the research; ***and***
- suggests that the research *places subjects or others at a greater risk of harm* (including physical, psychological, economic, or social harm) *than was previously known or recognized.*

Follow-up

All adverse events will be followed up according to good medical practices.

7.2.3 Reporting

Local events requiring expedited reporting, are submitted to the UTSW IRB through the UTSW eIRB and to the SCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; the NCI ADEERS, FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required.

If the event occurs on a multi-institutional clinical trial coordinated by the Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited

reporting. DSMC Chairperson reviews all serious adverse events within upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

	Telephone reports to: (Investigator: Arthur Frankel, MD, (office) 214-648-1579 UTSW SCC Data Safety Monitoring Committee Coordinator (if fax report is not available) within 1 working day to 214-648-7097.
	Written reports to: (Investigator: Arthur Frankel, MD, (fax) 214-6481578, 5323 Harry Hines Blvd,, Dallas, TX, 75390-8852 UTSW SCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-7018 or deliver to NB 2.418 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

1. Unexpected Adverse Events

Non-serious adverse events which are classified as both unexpected (in terms of nature, severity and frequency) and possibly related require reporting to the UTSW IRB within 10 working days of PI awareness.

2. SAEs

Local serious adverse events (SAEs) require reporting within 2 working days of PI awareness, or as described in the protocol.

3. Unanticipated Problems

Unanticipated problems, including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2:Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

8.0 Drug Formulation, Availability and Preparation

8.1 Availability

SL-401 is an experimental drug produced by Cancer Research Institute of Scott & White with approval of the FDA for investigational purposes (IND BB#11314).

8.2 Pharmaceutical Data

8.2.1 Formulation

SL-401 protein is supplied frozen in sterile 2 mL vials containing 1mg drug in 1 mL of 0.25M NaCl/5mM Tris, pH 8.0. Lot AT-2 or AT-1 will be used for this trial.

8.2.2 Reconstitution

Vials are to be thawed then drawn into a 3 cc syringe and filter sterilized using a 0.2μ filter. The drug is aliquoted into sterile screw top CryoTube vials for single doses and refrozen at -75^{o}C or below. The CryoTube vials will be labeled with the patient's identifying markers, the dose, the date on which it was prepared, and Caution: New Drug – Limited by Federal (or United States) law to investigational use. CryoTube frozen drug must be used within two weeks. On the day of administration, a single aliquot is thawed and diluted in saline. At Scott & White, either commercial saline or the Tris buffered saline will be used. The drug must be administered within one hour of thawing.

8.2.3 Storage and Stability

Intact vials should be stored at -75^{o}C or below and is stable for over 12 months. CryoTube refrozen drug is stable at -75^{o}C or below for over 2 weeks. The acceptable temperature variance is at -60^{o}C or lower. If a freezer registers -50^{o}C or higher then the drug will be transferred to an acceptable freezer.

8.2.4 Administration

The drug is to be given intravenously via a 3 cc plastic syringe as a 15min infusion daily for five days. $DT_{388}IL3$ will be administered through a Y-access on either a peripheral or central line with normal saline.

8.2.5 Procurement

Patients are registered with the study coordinator at (214) 648-5107. Following patient registration, the protocol administrator will notify Dr. Arthur Frankel (214) 648-1579 for dispensing of drug.

8.2.6 Drug-related Toxicities

Toxicities believed to be associated with SL-401 from completed and/or ongoing clinical trials include:

Frequent (>10%): anorexia, mild proteinuria,.dyspnea/wheezing, edema, fever, hypoalbuminemia, hypocalcemia, hypotension, nausea, rigors/chills, transaminase elevations, and vascular/capillary leak syndrome.

Less Frequent (>5% and ≤10%): vomiting and weight gain.

Rare (≤5%): alkaline phosphatase elevations, low fibrinogen, prolonged prothrombin time or partial thromboplastin time, abdominal cramping, anaphylaxis, anemia, bilirubin elevations, brusing, cardiac arrhythmia, cardiopulmonary arrest, coagulopathy, CPK changes, creatine kinase changes, creatinine changes, diarrhea, dizziness, fatigue, fluid overload/retention, headache, hemorrhage/bleeding, hyperglycemia, hypertension, hypokalemia, hypomagnesemia, hypoxia, infection (excluding sepsis, pneumonia, herpes), INR changes, leukopenia, lymphocytosis, lymphopenia, muscle weakness, neutropenia, organ insufficiency, pain, petechia, pneumonia, rash, renal failure, respiratory failure, skin lesions, thrombocytopenia, tubular necrosis, urine retention, and weakness.

9.0 Registration and Data Management Procedures

9.1 Registration

Patients may be registered by calling the study coordinator at (214) 648-5107 between 8:30 AM and 4:30 PM, Monday - Friday. If the patient meets the eligibility criteria, the study coordinator will register the patient with UT Southwestern Medical Center Hospital and Clinics. Patients must be registered before initiation of treatment in order to be eligible for the study.

9.2 Data Management Procedures

9.2.1 The Case Report Forms (CRF) will be completed by the study coordinator and submitted to the Study Chair and Sponsor, Arthur E. Frankel, M.D. and made available to the IRB and University of Texas Southwestern DSMC for review.

-Case Report Forms (CRF) to be available to study chair/PI every two weeks the patient is on study.

9.2.2 The signed informed consent form and “Authorization for Use or Disclosure of Protected Health Information for Research” will be obtained prior to the patient’s entry into the study.

10.0 Statistical Considerations

10.1 Design

This is a phase IB study designed to determine the safe dose of SL-401 (as defined in Schema IV) of SL-401 for treatment of patients with BPDCN. From this point on assuming no dose limiting toxicity (DLT) occurs, the dose will be administered to eleven patients. If two patients enrolled at the 12.5μg/kg dosel level experience DLT, the MTD has been exceeded and additional patients will be treated at the next lower dose level 10sameμg/kg. If two patients experience DLT, the MTD has been exceeded, and the study will be halted.

10.2 Feasibility

It is anticipated that approximately eleven patients will be needed for the dosing schedule for this phase IB evaluation of BPDCN. Based on the rarity of the disease and accrual to a previous SL-401 Phase I study of 15 patients per year, we expect this study to be completed within 2 years.

10.3 Analysis for Response

A total of eleven patients will be treated. Response measurements will be derived from the revised criteria of BPDCN response previously reported [1,2]. The lack of activity hypothesis (<5% response rate) will be rejected if 2 or more responses are seen (80% power for an alternative response rate of 30% at the 10% one-sided significance level). Since we have observed 3/3 CRs to date, we expect this hypothesis will be rejected.

Toxicities are dichotomized as none versus any, or none and mild versus moderate to severe. The rates of toxicity, overall response, and complete response, as well as their 95% confidence intervals, will be estimated at each dose level. Tables and graphs will be constructed to explore the association between toxicities and predictive variables, including pretreatment marrow blast index, pretreatment anti-SL-401 antibody level, blast IL3R level, and peak serum SL-401 concentration, serum SL-401 AUC, patient age, gender, serum creatinine, serum albumin, serum transaminase, number of circulating blasts, spleen size, skin disease, node disease, and visceral disease. The Kaplan-Meier methods will be used to estimate the time to the development of toxicity. Similarly, we will explore the association of SL-401 concentrations, anti-SL-401 concentrations, blast CD123 level, skin/node/organ disease, and marrow blast index with patient response. Results from this pilot phase 1B study will be used to develop multi-institutional phase II studies using designs that minimize the expected sample size under the null hypothesis or designs that allow a trade-off between response and toxicity.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Office of Research. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.3 Registration Procedures

All subjects must be registered with the Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Study Coordinator. To register a subject, call 214-648-5107 Monday through Friday, 8:30AM-4:30PM.

11.4 Data Management and Monitoring/Auditing

The SCC DSMC will serve as a primary DSMB. All trial processes from initial regulatory approvals to final data submission must be scrutinized to ensure compliance with federal, institutional and protocol-specific guidelines, accuracy of data capture, and appropriate attention to safety. Monitoring of adverse events, case report forms and overall study conduct is continuously performed at the level of the disease oriented team, and, more formally, by scheduled audits performed by the Quality Assurance and Education Coordinator (QAC) under the authority of the DSMC.

11.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.5.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

11.5.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case

of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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