MD Anderson IND Sponsor Cover Sheet

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TABLE OF CONTENTS

1. INTRODUCTION

1.1 Outcomes of Acute Lymphoblastic Leukemia (ALL) in Adults

Significant improvements in outcome for childhood acute lymphoblastic leukemia (ALL) have been observed, with complete response (CR) rates exceeding 90% with modern chemotherapy regimens.[1,2] At least 70% of children with ALL can be cured. Adult ALL however has a worse outcome. Expected CR rates are 80% to 90%, and long-term event-free survival (EFS) rates are 20% to 40%.[3-7] Prognosis is influenced by age, performance status, organ function, white blood cell count, ALL phenotype (CALLA, T-cell, B-cell, Burkitt's or Burkitt's-like), karyotype [t(1; 19), t(4; 11), Philadelphia (Ph) chromosome], and time to achieve CR.

The longer-term results of hyper-CVAD in adult ALL have been reported[8,9]. Overall, the group had a median age of 40 years (range 15-90 years); 20% of the patients were aged 60 or older.[9] The majority of patients were considered high-risk for systemic relapse (74%) or central nervous system (CNS) relapse (55%). Compared to the VAD (vincristine, doxorubicin, dexamethasone) program, the outcome with hyper-CVAD was significantly improved with respect to CR rate and overall survival.[8,9]

The overall CR rate with hyper-CVAD for all subtypes of ALL (n=288) was 92% with an induction mortality of 5% (all due to infections). Eleven percent of the patients required 2 courses to achieve CR; only 3% of the patients failed to achieve a remission with persistence of the leukemia. Central nervous system relapse was low, with a 7% incidence in low-risk patients (given 4 prophylactic intrathecal [IT] treatments), 1% in high-risk patients (16 prophylactic ITs), and 6% in patients with unknown CNS relapse risk (8 prophylactic ITs).[9] The 5-year continuous CR rate was 35% with a 5-year survival of 36%. On multivariate analysis, pre-treatment factors associated with a shorter survival included older age, poor performance status, presence of hepatomegaly, high leukocyte count ($\geq$ 50 x 10^9/L), low platelet count, and Ph-positive disease. When compared to other published standard regimens of MSKCC,[5] SWOG,[6] Hoelzer et al,[4] and Larson et al,[7] the outcome was comparable even though the MDACC patients were older and prognostically less favorable.

Current outcomes of salvage chemotherapy for ALL are poor, with less than half of patients achieving a second CR, with rates varying based on prior therapy and duration of first remission.[11,12] CR rates are even lower for patients with multiply refractory disease. Further intensification of chemotherapy has not proved to be effective.[13] Novel monoclonal antibodies have been introduced to the armamentarium of therapies of relapsed/refractory ALL inducing responses in about 40-50% of patients with a median survival of 6 to 8 months. While allogeneic stem cell transplantation (allo-SCT) offers a chance for long-term remission and cure, only a small percentage of patients could be bridged to allo-SCT with current therapies. Given the poor outcomes for patients with relapsed/refractory ALL, novel agents and combinations capable of achieving remission to allow for potentially curative allogeneic stem cell transplantation SCT are needed.

1.2 CD123 and Tagraxofusp in ALL

CD123, the interleukin-3 (IL-3) receptor α-chain subunit binds IL-3 with high affinity when co-expressed with the β-subunit. IL-3, mainly produced by T-lymphocytes, plays a critical role in leukomogenesis through enabling leukemic cells to escape programmed cell death and inhibiting their apoptosis.[14] CD123, previously reported to have a low to absent normal hematopoietic stem cell expression, is expressed at various levels in hematologic malignancies, including hairy cell

leukemia, acute myeloid leukemia (AML), blastic plasmacytoid dendritic cell neoplasm (BPDCN) and others. Due to its differential overexpression on leukemic cells compared to their normal precursors as well as its expression on both cancer stem cells (CSCs) and leukemic blasts, the cell surface receptor CD123 has emerged as a promising target of therapy.[15] In ALL, clinical and preclinical studies suggest significant overexpression of CD123 on leukemic cells. An early analysis by Djokic and colleagues in 2009 reported on the CD123 expression in 95 pediatric and 24 adult patients with B-ALL, showing 31% strong CD123 expression on B-ALL blasts, 61% moderate expression and 8% absent expression.[16] In contrast, early B-cell precursors, intermediate B-cells and mature B-lymphocytes displayed only absent or low CD123 expression. Hassanein et al. confirmed these findings and, particularly, analyzed the normal compartment of B-cell precursors, as well as B-ALL leukemic blasts. They showed that early B-cell CD3+ precursors do not express CD123, while more mature CD34+ B-cell elements express CD123. In B-ALL, CD123 expression was observed in 89% of cases, 80% concomitantly with CD34 expression and 9% in the absence of CD34 expression. Interestingly, in the majority of B-ALL patients, CD123+/CD34+ cells were observed post-chemotherapy. In a recent study of 183 patients with B-ALL, CD123 was found to be overexpressed in 90% of patients with B-ALL, both in patients with Philadelphia-chromosome positive ALL (86%) and those with Philadelphia-chromosome negative ALL (97%).[17] The pronounced CD123 expression in B-ALL offers an opportunity for possible therapeutic targeting.

Tagraxofusp, formerly known as SL-401, is a novel biologic targeted therapy comprised of recombinant human IL-3 joined to a truncated diphtheria toxin (DT). In preclinical studies, SL-401 has demonstrated anti-tumor activity against both leukemic blasts as well as leukemia CSCs, both in vitro and in vivo.[18] In fact, SL-401 has been investigated in clinical trials for patients with BPDCN and other hematologic malignancies. In a multicenter, open-label study of 47 patients with BPDCN (median age, 70 years; 32 previously untreated), patients received daily infusions of tagraxofusp (7 or 12 µg/kg) on days 1 to 5 of each 21-day cycle until disease progression or unacceptable toxicity.[19] At a median follow-up of 19 months, of the 29 untreated patients who received the 12 µg/kg dose, 90% responded and 72% achieved CR; almost half of responding patients proceeded to allo-SCT or autologous SCT (3 patients). The 24-month overall survival for responding patients was 52%. Of the 15 patients with R/R disease, 67% responded and 1 patient proceeded to allo-SCT; median overall survival was 8.5 months. Toxicities included elevated liver enzymes, hypoalbuminemia, edema, and thrombocytopenia. Capillary leak syndrome (CLS) occurred in 18% of patients, resulting in 2 deaths. In support of this, SL-401 received FDA approval for patients with BPDCN as a single-agent on Dec 21, 2018. In addition to BPDCN, tagraxofusp is also being investigated, as a single agent, in several ongoing clinical trials in AML with positive measurable residual disease (MRD), myelofibrosis and chronic myelomonocytic leukemia. In addition to the single agent experience, tagraxofusp is also being investigated in the combination setting at our institution such as the combination of tagraxofusp with azacitidine in AML. Thus, across multiple tumor types and as single agent or in combination, we have acquired extensive experience with the administration of tagraxofusp and have established its safety profile and efficacy in prior studies.

1.3.4 Summary

Overall, the urgent need for novel therapies in R/R ALL, the significant overexpression of CD123 in leukemic CSCs and blasts of ALL, the promising efficacy of tagraxofusp in targeting CD123 in hematologic malignancies, and our extensive experience using this agent warrant further investigation of tagraxofusp in R/R ALL to improve on the modest outcomes currently achieved with salvage chemotherapy in this setting. We, therefore, propose to assess the safety and efficacy of tagraxofusp in combination with low-intensity chemotherapy with mini-hyper-CVD in R/R ALL.

2. STUDY OBJECTIVES

2.1. Primary Objective: To evaluate the overall response rate (CR + CR with inadequate count recovery [CRi]) of the regimen within 3 cycles

2.2 Secondary Objectives

- Evaluate other clinical efficacy endpoints (CR rate, minimal residual disease [MRD] negativity, duration of response [DOR], relapse-free survival [RFS] overall survival [OS])
- Determine the proportion of patients proceeding to allo-SCT
- Determine the safety of the combination regimen.

2.3 Exploratory Objectives

- To determine CD123 expression levels pre- and post-therapy
- To correlate baseline CD123 expression with response rates and duration of response
- To evaluate change in apoptotic protein expression and alterations in cellular signaling pathways using CyTOF
- To determine baseline gene expression profile in order to identify ALL subtypes and correlate with clinical outcomes and response to single-agent tagraxofusp

See Appendix B for details of correlative study plan.

3. SELECTION OF PATIENTS

Patients will be selected from those referred to the Leukemia department at MD Anderson Cancer Center through the normal of process of referral. Eligible patients will be registered after the process of consenting on the MD Anderson protocol and data monitoring system.

3.1 Inclusion Criteria

1. Patients 18-70 years of age with relapsed/refractory CD123+ B- or T-cell ALL, lymphoblastic lymphoma, or mixed phenotype acute leukemia or biphenotypic leukemia with a B-cell or T-cell immunophenotype .
   - *CD123 positivity may be confirmed by either flow cytometry or immunohistochemistry.*
   - *Patients with B-cell ALL should have previously received or be ineligible for blinatumomab, inotuzumab ozogamicin and tisagenlecleucel*

2. Performance status ≤ 2 (ECOG Scale)

3. Adequate liver and renal function as defined by the following criteria:
   a) Total serum bilirubin $\leq$ 1.5 x upper limit of normal (ULN), unless due to Gilbert's syndrome, in which case patients are eligible as long as direct bilirubin ≤2 x ULN
   b) Alanine aminotransferase (ALT) $\leq$ 2.5 x ULN, unless due to disease involvement of the liver or hemolysis, in which case an ALT ≤10 x ULN is acceptable, OR

c) Aspartate aminotransferase (AST) ≤ 2.5 x ULN, unless due to disease involvement of the liver or hemolysis, in which case an ALT ≤10 x ULN is acceptable
d) Creatinine clearance ≥ 60 mL/min

4. Serum albumin ≥3.2 g/dL (32 g/L). *Albumin infusions are not permitted in order to enable eligibility.*

5. For females of childbearing potential, a negative pregnancy test must be documented within 1 week of starting treatment

6. Female and male patients who are fertile must agree to use an effective form of contraception (birth control methods while on study, such as birth control pills or injections, intrauterine devices (IUDs), or double-barrier methods (for example, a condom in combination with spermicide) with their sexual partners for 4 months after the end of treatment

7. Signed informed consent

8. Willingness and ability to adhere to study visit schedule and other protocol requirements, including follow-up for survival assessment

3.2 Exclusion Criteria

1. Active serious infection not controlled by oral or intravenous antibiotics.

2. Known active CNS leukemia

3. Diagnosis of Philadelphia chromosome-positive ALL or Burkitt leukemia/lymphoma

4. Active GVHD

5. Active secondary malignancy other than skin cancer (e.g., basal cell carcinoma or squamous cell carcinoma) that in the investigator's opinion will shorten survival to less than 1 year.

6. Known active hepatitis B or C infection, or active/uncontrolled HIV infection or AIDS.

7. Clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction, unstable angina or stroke within 6 months prior to study entry, uncontrolled hypertension (diastolic blood pressure >90mmHg; systolic >140mmHg) or clinically significant arrhythmias not controlled by medication).

8. Patients with a cardiac ejection fraction (as measured by either MUGA or echocardiogram) less than the lower limit of normal

9. No clinically significant abnormalities on 12-lead electrocardiogram

10. Concomitant use of calcineurin inhibitors in 4 weeks prior to the start of therapy

11. Uncontrolled, clinically significant pulmonary disease (e.g., chronic obstructive pulmonary disease, pulmonary hypertension) that in the opinion of the Investigator would put the patient at significant risk for pulmonary complications during the study.

12. Persistent clinically significant toxicities Grade ≥2 from previous chemotherapy (excluding alopecia, nausea, and fatigue).

13. Treatment with any investigational antileukemic agents or chemotherapy agents in the last 7 days before study entry, unless full recovery from side effects has occurred or patient has rapidly progressive disease judged to be life-threatening by the investigator. *Exception*: Treatment with hydroxyurea and/or dexamethasone are allowed prior to study treatment, without window of exclusion.

11. Pregnant and lactating women will not be eligible; women of childbearing potential should have a negative pregnancy test prior to entering on the study and be willing to practice methods of contraception for 4 months after last study treatment. Women do not have childbearing potential if they have had a hysterectomy or are postmenopausal without menses for 12 months. In addition, men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control for 4 months after last study treatment.

4. TREATMENT OF SUBJECTS

4.1 Variations in dose reductions of the individual chemotherapy or the administration of tagraxofusp or supportive care dose schedules other than those suggested below are allowed in the best interest of patients. Such patients should be discussed with the principal investigator. Dose escalations of chemotherapy above those outlined in the protocol; however, are not allowed. Variations in infusion times due to minor differences in IV bag overfill/underfill and institutional procedure on flushing chemotherapy lines will not result in protocol deviation.

4.2 **Treatment Overview** – The treatment will start with of an induction phase (Cycle 1) consisting of the administration of tagraxofusp single agent at a dose of 12 µg/kg daily for 5 days of a 21-day cycle. Following the 21-day induction phase, the treatment cycles consisting of the combination of tagraxofusp and chemotherapy with mini-hyper-CVD will be administered (Cycles 2-5 with tagraxofusp plus chemotherapy; cycles 6-9 with chemotherapy without tagroxofusp). In each of these cycles, tagraxofusp will be given at the dose of 9 µg/kg daily for the first 3 days followed by administration of mini-hyper-CVD or mini-methotrexate plus cytarabine on days 4 onwards. Each of these combination cycles (Cycle 2+) is 28 days. The mini-hyper-CVD chemotherapy regimen consists of a total of 8 cycles of mini-hyper-CVD [cyclophosphamide (150 mg/m2 every 12 h for 3 days), vincristine (2 mg flat dose for 2 doses), and dexamethasone (20 mg for 8 total doses per cycle) without anthracycline] alternating with high-dose methotrexate (250 mg/m2 x 1) and cytarabine (0.5 g/m2 given every 12 hours for 2 days) administered approximately every 28 days (or later to allow for recovery from myelosuppression or infection). Tagraxofusp will be administered for a maximum of 5 cycles (Cycles 1-5) during induction/consolidation. On cycles containing tagraxofusp and chemotherapy (Cycles 2-5), chemotherapy will begin on day 4; on cycles not containing tagraxofusp (Cycles 6-9), chemotherapy will begin on day

1. Rituximab and intrathecal chemotherapy will be given for the first 4 combination cycles (Cycles 2-5).

4.3 **Cycle 1** – Patients will receive tagraxofusp 12 µg/kg daily for 5 days. The patients will remain hospitalized up until a minimum of 24 hours after the last dose of tagraxofusp. Hospital stay may be prolonged in patients with infections or other issues requiring inpatient stay. Cycle 1 is 21 days in length.

Use of hydroxyurea and/or dexamethasone during cycle 1 is allowed on a patient-by-patient basis during cycle 1 if deemed in the best interest of the patient and after discussed with the PI.

4.4 **Cycles 2-5** – Cycles 2-5 are anticipated to be 28 days in length. Tagraxofusp will be given at a dose of 9 µg/kg daily for the first 3 days followed by administration of mini-hyper-CVD or mini-methotrexate plus cytarabine on days 4 onwards. Patients will be admitted for tagraxofusp and for the mini-hyper-CVD / methotrexate and cytarabine regimen. The patients will remain hospitalized up until the completion of chemotherapy. Hospital stay may be prolonged in patients with infections or other issues requiring inpatient stay.

4.5 **Cycles 6-9** – Cycles 6-9 are anticipated to be 28 days in length. No tagraxofusp will be given with these cycles. Mini-hyper-CVD or mini-methotrexate plus cytarabine will begin on day 1. Patients will be admitted for the mini-hyper-CVD / methotrexate and cytarabine regimen. The patients will remain hospitalized up until the completion of chemotherapy. Hospital stay may be prolonged in patients with infections or other issues requiring inpatient stay.

At anytime while enrolled in this trial, patients may be referred for SCT at the discretion of the treating physician.

4.6 Alteration of regimen for patients achieving response to tagraxofusp monotherapy

Patients who achieve CR or CRi with tagraxofusp monotherapy after cycle 1 will continue with receive tagraxofusp monotherapy (12 µg/kg daily for 5 days) rather than proceeding to additional cycles with tagraxofusp plus low-intensity chemotherapy. These patients will continue to receive cycles of tagraxofusp monotherapy (up to 5 total cycles) for as long as they remain in CR/CRi. Following these 5 cycles of tagraxofusp monotherapy, they will proceed with maintenance therapy as below.

4.7 Tagraxofusp

- See Appendix A for management of tagraxofusp
- For details of tagraxofusp preparation and other pharmacologic consideration, please see the corresponding investigator brochure for tagraxofusp, as well as pharmacy manuals for the frozen and lyophilized formulations of tagraxofusp.
- Expired or unused study drug will be disposed per institutional protocols
- Patients will receive the following premedication approximately 60 minutes before each tagraxofusp infusion:
    - Acetaminophen 650 mg orally (PO)

- Diphenhydramine 50 mg intravenously (IV) (or equivalent dose of another H1-histamine antagonist)
- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid)
- Famotidine 20 mg IV (or an equivalent dosage of another H2-histamine antagonist)

- Pre-treatment Criteria for Tagraxofusp
  - Prior to the initiation of the first dose of tagraxofusp in Cycle 1, serum albumin must be ≥ 3.2 g/dL
  - Patients with serum albumin 3.2 to 4.0 g/dL should receive 25g intravenous albumin prior to Cycle 1, Day 1 dose of tagraxofusp
- Withhold tagraxofusp on a given treatment day if any of the following occur:
  - Serum albumin < 3.5 g/dL (see APPENDIX A for management of suspected CLS)
  - If serum albumin has fallen more than 0.5 g/dL below the level measured on the first treatment day of the cycle (see Appendix A for Management of tagraxofusp-related toxicites,)
  - AST > 5x ULN or ALT > 5x ULN
  - Serum creatinine > 2x ULN
  - Signs of clinically significant capillary leak syndrome, defined as:
    - HR ≥ 130 or ≤ 40 bpm
    - SBP ≥ 160 or ≤ 80 mmHg
    - Body temperature ≥ 38.0 C
    - Increase in body weight by ≥ 1.5 kg over the weight measured prior to treatment on the prior day
- Initiation of mini-hyper-CVD or methotrexate/cytarabine will also be delayed if tagraxofusp is delayed as above. Mini-hyper-CVD and methotrexate/cytarabine should not begin until the day following the last planned dose of tagraxofusp for a given cycle.
- Tagraxofusp must be given in the inpatient setting during cycle 1, along with monitoring for at least 24 hours after the last infusion. For all patients receiving cycles of chemotherapy plus tagraxofusp, tagraxofusp will be given in the inpatient setting, along with 24 hour monitoring as above. For subsequent cycles of tagraxofusp monotherapy (e.g. patients who achieve CR/CRi with cycle 1 and continue to receive tagraxofusp monotherapy as consolidation, or in patients receiving tagraxofusp monotherapy in maintenance), tagraxofusp may be given either the inpatient setting or in a suitable outpatient ambulatory care setting that is equipped with appropriate monitoring for patients with hematopoietic malignancies undergoing treatment. These patients must be monitored for a minimum of 4 hours following each infusion.

4.8 Mini-hyper-CVD Regimen

1. General Considerations
   - The mini-hyper-CVD will alternate with methotrexate and cytarabine administered on 28 (if count recovery allows) or later day cycle (as count recovery allows).
   - Anti-emetic therapy with each course of intensive chemotherapy as needed.
   - Filgrastim product (G-CSF) will be administered with each course after the completion of chemotherapy. Pegfilgrastim product may replace filgrastim product (G-CSF).
   - Next cycle may be started when granulocytes > 1.0 x 10^{9}/L and platelets ≥ 50 x 10^{9}/L. Cycles may be started with dose reductions prior to full platelet recovery, if the treatment is delayed (e.g., greater than 28 days from last cycle).

- Prophylactic antibiotics may be given with each course until neutrophil recovery to 500/μL or greater (or other antibiotics if being treated for active infection). Suggestions include: Levaquin 500 mg po daily, trimethoprim-sulfamethoxazole double strength one tablet p.o. b.i.d. or other appropriate antibacterial agent. Caspofungin or other appropriate antifungal agent. Valacyclovir 500 mg p.o. daily or acyclovir 200 mg p.o. b.i.d. or other appropriate antiviral agent.
- Omit azoles day -1, same day, and day after vincristine.
- In general 8 cycles of chemotherapy (4 mini-hyper-CVAD, 4 methotrexate plus cytarabine) will be administered in approximately 4 week intervals (depending on the recovery of blood counts. Modifications thought to be in the best interest of the patient are allowed after discussion with the principal investigator. Patients will be followed indefinitely for relapse and survival.
- For patients with CD20 expression (≥ 20% by flow cytometry) up to 2 doses of rituximab 375 mg/m^2 may be added in cycles 2-5 (8 doses total).
- Methotrexate dose will be adjusted as indicated below for pleural effusions.

2. Mini-Hyper-CVD with tagraxofusp [Cycles 2 and 4]:
   - Tagraxofusp at a dose of 9 μg/kg daily IV on days 1-3
   - Cyclophosphamide (CTX) 150 mg/m^2 intravenously (IV) over 3 hrs (± 1 hour) every 12 hrs x 6 doses days 4-6
   - MESNA 300 mg/m^2/d IV continuous infusion daily for 24 hrs (± 4 hours), starting approximately 1 hour prior to CTX and completing by approximately 12 hrs after the last dose of CTX.
   - Vincristine 2 mg IV on day 4 (± 3 days) and day 15 (± 3 days). Vincristine is not myelosuppressive and may be given while patients are receiving filgrastim product (G-CSF); no known adverse effects have been observed with the 2 agents given together.
   - Dexamethasone 20 mg IV or p.o. daily on days 4-7 (± 3 days) and days 14-17 (± 3 days).
   - Filgrastim product (G-CSF) 10 mcg /kg (rounded) subcutaneously daily (or 5 mcg /kg twice daily) until post-nadir granulocytes > 1.0 x 10^9/L. Filgrastim product (G-CSF) may be stopped earlier for bone pain or other related toxicity. Minimum time allowed between courses is 14 days. Pegfilgrastim product may replace filgrastim product (G-CSF) at a dose of 6 mg SQ on Day 8 (± 3 days).
   - For patients with CD20 expression (≥ 20% by flow cytometry) Rituximab 375 mg/m^2 may be added on days 4 (± 3 days) and 14 (± 3 days). In patients receiving rituximab all therapy can be moved back 1 day if needed (i.e. day 1 starts day 2, day 2 starts day 3, etc.).
   - CNS prophylaxis: Methotrexate 12 mg intrathecally (6 mg via Ommaya reservoir) on day 5 (± 3 days). Cytarabine 100 mg intrathecally on day 10 (± 3 days) for a total of 8 IT doses. These are generally given on cycles 2-5 but if one or more IT treatments is missed it can be made up on a later cycle. Administer in 3 to 5 cc of preservative-free normal saline.

3. Mini-Hyper-CVD without tagraxofusp [Cycles 6 and 8]:
   - Cyclophosphamide (CTX) 150 mg/m^2 intravenously (IV) over 3 hrs (± 1 hour) every 12 hrs x 6 doses days 1-3

- MESNA 300 mg/m^2/d IV continuous infusion daily for 24 hrs (± 4 hours), starting approximately 1 hour prior to CTX and completing by approximately 12 hrs after the last dose of CTX.
- Vincristine 2 mg IV on day 1 (± 3 days) and day 11 (± 3 days). Vincristine is not myelosuppressive and may be given while patients are receiving filgrastim product (G-CSF); no known adverse effects have been observed with the 2 agents given together.
- Dexamethasone 20 mg IV or p.o. daily on days 1-4 (± 3 days) and days 11-14 (± 3 days).
- Filgrastim product (G-CSF) 10 mcg /kg (rounded) subcutaneously daily (or 5 mcg /kg twice daily) until post-nadir granulocytes > 1.0 x 10^9/L. Filgrastim product (G-CSF) may be stopped earlier for bone pain or other related toxicity. Minimum time allowed between courses is 14 days. Pegfilgrastim product may replace filgrastim product (G-CSF) at a dose of 6 mg SQ on Day 5 (± 3 days).

4. Methotrexate and cytarabine with tagraxofusp [Cycles 3 and 5]
    - Tagraxofusp at a dose of 9 µg/kg daily IV on days 1-3
    - Methotrexate (MTX) 50 mg/m^2 IV over 2 hrs (± 1 hour) followed by 200 mg/m^2 over 22 hrs on day 4. Total duration of administration is 24 hours (2 plus 22 hours) (± 3 hours).
    - Cytarabine 0.5 g/m^2 IV over 3 hrs (± 1 hour) every 12 hrs for 4 doses on days 5 and 6.
    - Leucovorin rescue 50 mg IV or PO followed by 15 mg IV or PO every 6 hours for 8 doses beginning 12 hrs (± 3 hrs) post MTX completion, i.e. approximately 36 hours from start of MTX.
    - Check MTX levels around time 0h, 24h and 48h post completion of MTX unless methotrexate cleared:
        - if > 20 µM at time 0, hold cytarabine and repeat level; if continues to be > 20 µM reduce cytarabine to 0.25 g/m^2 IV over 2 hours every 12 hours for 4 doses on days 2 and 3. Begin leucovorin rescue as described above.
        - if > 1 µM at 24hrs or > 0.1 µM at 48 hours, increase leucovorin rescue to 50 mg IV or PO every 6 hrs until serum methotrexate level is < 0.1 µM. Clearance to levels 0.15 µM or less is acceptable in patients with normal renal function.
        - Leucovorin rescue may be increased further for elevated methotrexate levels or delayed clearance
    - Filgrastim product (G-CSF) 10 mcg/kg (rounded) subcutaneously daily (or 5 mcg /kg twice daily) until post-nadir granulocytes ≥ 1.0 x 10^9/L. Filgrastim product (G-CSF) may be stopped earlier for bone pain or other related toxicity. Minimum time allowed between courses is 14 days (e.g., day 14). Pegfilgrastim product may replace filgrastim product (G-CSF) at 6 mg SQ on Day 6 (± 3 days).
    - For patients with CD20 expression (≥ 20% by flow cytometry) Rituximab 375 mg/m^2 may be added on days 4 (± 3 days) and 11 (± 3 days). In patients receiving rituximab all therapy can be moved back 1 day if needed (i.e. day 1 starts day 2, day 2 starts day 3, etc.).
    - CNS prophylaxis: cytarabine 100 mg day 8 (± 3 days) and methotrexate 12 mg intrathecally (6 mg via Ommaya reservoir) day 11 (± 3 days) of cycle 3 and 5 for a total of 8 IT doses. These are generally given on cycles 2-5 but if one or more

IT treatments is missed it can be made up on a later cycle. Administer in 3 to 5 cc of preservative-free normal saline

5. Methotrexate and cytarabine without tagraxofusp [Cycles 7 and 9]
    - Methotrexate (MTX) 50 mg/m^2 IV over 2 hrs (± 1 hour) followed by 200 mg/m^2 over 22 hrs on day 1. Total duration of administration is 24 hours (2 plus 22 hours) (± 3 hours).
    - Cytarabine 0.5 g/m^2 IV over 3 hrs (± 1 hour) every 12 hrs for 4 doses on days 2 and 3.
    - Leucovorin rescue 50 mg IV or PO followed by 15 mg IV or PO every 6 hours for 8 doses beginning 12 hrs (± 3 hrs) post MTX completion, i.e. approximately 36 hours from start of MTX.
    - Check MTX levels around time 0h, 24h and 48h post completion of MTX unless methotrexate cleared:
        - if > 20 μM at time 0, hold cytarabine and repeat level; if continues to be > 20 μM reduce cytarabine to 0.25 g/m^2 IV over 2 hours every 12 hours for 4 doses on days 2 and 3. Begin leucovorin rescue as described above.
        - if > 1 μM at 24hrs or > 0.1 μM at 48 hours, increase leucovorin rescue to 50 mg IV or PO every 6 hrs until serum methotrexate level is < 0.1 μM. Clearance to levels 0.15 μM or less is acceptable in patients with normal renal function.
        - Leucovorin rescue may be increased further for elevated methotrexate levels or delayed clearance
    - Filgrastim product (G-CSF) 10 mcg/kg (rounded) subcutaneously daily (or 5 mcg /kg twice daily) until post-nadir granulocytes ≥ 1.0 x 10^9/L. Filgrastim product (G-CSF) may be stopped earlier for bone pain or other related toxicity. Minimum time allowed between courses is 14 days (e.g., day 14). Pegfilgrastim product may replace filgrastim product (G-CSF) at 6 mg SQ on Day 4 (± 3 days).

4.9 Intrathecal Treatments

- Patients should receive 8 total doses of intrathecal chemotherapy (2 intrathecal injections of methotrexate and cytarabine with cycles 2-5 until the total number reached)
- If the patient has been previously treated, and has had prior intrathecal therapy, or prior CNS disease, discuss management of CNS with the principal investigator.
- If active CNS disease: Consider methotrexate alternating with cytarabine twice weekly until CSF clear; then once weekly for 4 weeks, then every other week for 4 weeks, then monthly for 4 months. Consider radiotherapy (XRT) to the base of the skull, particularly with cranial nerve root involvement (cranial nerve palsies). Alternative methods of treating CNS disease are allowed if appropriate for the patient (e.g., intrathecal liposomal cytarabine, or others). Modifications to the regimen thought to be necessary for administration of XRT are allowed after discussion with the principal investigators.
- Concomitant intrathecal chemotherapy should be avoided, if possible, on the days of administration of intravenous methotrexate and cytarabine (odd cycles).

4.10 Suggested Standard Dose Reductions/Modifications:

- Vincristine 1 mg IV (50% reduction) if:
    - Bilirubin > 2 mg/dl and ≤ 3 mg/dl
    - Clinically significant grade 2 peripheral neuropathy persisting greater than 2 weeks.
    - Eliminate vincristine for grade 3-4 peripheral neuropathy, including grade 3-4 ileus suspected to be related to vincristine, or bilirubin > 3 mg/dL.
- Methotrexate:
    - Consider reduction by 25%-50% for grade 3 or worse mucositis with previous methotrexate course.
    - Reduce by 50% for calculated creatinine clearance 10-50 ml/min, if < 10 ml/min, hold methotrexate.
    - Reduce by 25% to 75% for delayed excretion and/or nephrotoxicity with previous methotrexate course.
    - Reduce by 50% for pleural effusion or ascites (drain effusion if possible).
- Tagraxofusp
    - See Appendix A for management of tagroxofusp
- Other modifications of drug schedules may be implemented if judged to be in the best clinical interest of the patient after discussion with PI or at the discretion of the treating physician. This includes delays in chemotherapy cycles because of persistent myelosuppression, other side effects, patient request, or other reasons.
- Dose reductions exceeding those above or in other agents, e.g., leucovorin, antibiotics, antiemetics, etc., are allowed after discussion with the Principal Investigator.

4.11Maintenance

- Patients may be moved to the maintenance phase prior to completion of 9 cycles of induction/consolidation if significantly intolerant to prior therapy after discussion with the Principal Investigator.
- Maintenance chemotherapy is contained of POMP cycles (6-mercaptopurine (6-MP) + methotrexate (MTX) + vincristine + prednisone) and tagraxofusp cycles. A cycle of tagraxofusp will be given after every 3 Cycles of POMP for a total of 15 cycles of maintenance therapy. POMP maintenance will be given on Cycles 1-3, 5-7, 9-11, 13-15, and Tagraxofusp maintenance will be given on Cycles 4, 8, and 12.
    - POMP cycles
        - 6-MP 50 mg PO three times daily (TID), change of frequency to once daily dose is permitted and will not result in a deviation.
        - MTX 20mg/m2 (rounded) PO weekly
        - Vincristine 2 mg IV day 1 approximately every 28 days
        - Prednisone 200 mg PO daily about days 1 to 5 approximately every 28 days, starting with vincristine (if given). Shift of prednisone from days 1-5 to days 2-6 is permitted and will not result in a deviation.
    - Tagraxofusp cycles
        - Tagraxofusp will be given at a dose of 12 µg/kg daily IV on days 1-5. These cycles will be approximately 28- days in length.

Suggested maintenance chemotherapy dose adjustments as below:

Table 1: Maintenance

Level	MTX (mg/m^2) (rounded)	6-MP (mg/d)	Vincristine (mg)	Prednisone (mg)
0	20	150	2	200
-1	15	100	1	100
-2	10	50	0	50
-3	5	50	0	0

- Dose adjustments for myelosuppression include MTX and 6-MP, but not vincristine or prednisone (the latter should remain 200 mg unless steroid myopathy or other uncontrolled significant toxicity occurs). Titrate to keep granulocytes ≥ 1 x 10^9 /L and platelet count ≥ 50 x 10^9 /L.
- Methotrexate
    - Decrease by one dose level for mucositis > grade 2.
    - Decrease by one dose level for bilirubin > 2.5 or elevation of transaminases ≥ 5 x upper limit of normal.
    - Hold if granulocyte count nadir < 0.5 x 109 /L or platelets < 10 x 109 /L, resume with decrease in one dose level or lower depending on duration of cytopenias.
- Mercaptopurine (6-MP)
    - Decrease by one dose level for bilirubin > 2.5 mg/dL or elevation of transaminases ≥ 5 x upper limit of normal.
    - Hold if granulocyte count nadir < 0.5 x 109 /L or platelets < 10 x 109 /L, resume with decrease in one dose level or lower depending on duration of cytopenias.
- Vincristine
    - Decrease by one dose level for ≥ grade 2 peripheral neuropathy persisting for more than 2 weeks.
    - Discontinue for grade 3 or greater peripheral neuropathy.
- Note that the dose adjustments of POMP are guidelines, and the dosing needs to be individualized to the patient, as differential toxicities between 6-MP and methotrexate may be difficult to discern.
- Continued antiviral prophylaxis to prevent herpes zoster is strongly encouraged. Consider antifungal prophylaxis during days of prednisone. Consider PCP prophylaxis.

4.12 Definition of DLT –

- Any treatment-related death
- AST or ALT >= 3 x ULN in the setting of total bilirubin >= 2 x ULN, without findings of cholestasis, and no other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury
- Grade 4 neutropenia lasting ≥42 days from start of cycle in the absence of evidence of active leukemia, regardless of investigator attribution.
- Grade ≥ 3 non-hematologic toxicity not clearly resulting from underlying leukemia (and unrelated to intercurrent illness, or concomitant medications) that do not improve to < grade 2 within 72 hours with treatment interruption and maximal medical therapy and that occur within the first 3 cycles (i.e., 28 days after beginning of cycle 3) should be considered a DLT with the following pre-specified exceptions:

- Grade 3 alopecia.
- Grade 3 fatigue, asthenia, fever, anorexia or constipation lasting < 7 days.
- Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization.
- Infection, bleeding or other expected direct complication of cytopenias due to active underlying leukemia.
- Grade 3 infusion reaction including cytokine release syndrome (CRS) or capillary leak syndrome (CLS), if successfully managed and which resolves within 72 hours
- Grade 3 or 4 tumor lysis syndrome if it is successfully managed clinically and resolves within 7 days without end-organ damage.
- Grade 4 electrolyte abnormalities that resolve within 72 hours

4.13 Safety lead-in

We will enroll 6 patients in a safety lead-in to evaluate the safety of tagraxofusp in combination with hyper-CVD. These patients will count toward the phase II analysis. The regimen will initially be explored in 6 eligible patients. If none or only one of the 6 patients experiences DLT in the first 3 cycles attributable to the treatment components, this study will continue to accrue patients. If DLT attributable to the components is observed in 2 or more of these initial 6 patients, no further patients will be treated. A lower dose of the combined agents would be assessed based on the investigators' decision, which will be implemented with amendment to the study.

5. CONCOMITANT MEDICATIONS

Concomitant medications will be documented in the subject's electronic medical record but will not be entered into the case report form (Prometheus).

Medications that inhibit platelet function (i.e.,aspirin, dipyridamole, epoprostenol, eptifibatide, clopidogrel, cilostazol, abciximab, ticlopidine, and any non-steroidal anti-inflammatory drug) or Anticoagulants (warfarin, heparin/low molecular weight heparin [e.g., danaparoid, dalteparin, tinzaparin, enoxaparin]) should be avoided as much as possible during induction and consolidation due to expected thrombocytopenia.

Exceptions include low-dose warfarin for prophylaxis to prevent catheter thrombosis, and for heparin-flushes for IV lines. If patients develop deep vein thrombosis during the course of therapy or are receiving anticoagulation for indications such as recent thrombosis or artificial heart valves these drugs may be continued with close monitoring of the patients.

Irradiation of extramedullary disease may be performed at the discretion of the treating physician after consultation with the study PI.

Concomitant hydroxyurea is allowed during cycle 1 if needed to control peripheral white blood cell count. Use of hydroxyurea in this period should be discussed with the PI.

Patients may be concurrently enrolled in supportive care clinical trials. Other investigational agents that are used for treatment of other cancers will not be allowed.

6. STUDY PROCEDURES

Table 2: Study Procedures

		Chemotherapy and/or Tagraxofusp									Maintenance	Follow-up
	Pre-Rx Within 14 days of start treatment	1	2	3	4	5	6	7	8	9	Cycles 1-15	30 days after last dose
Informed consent	X											
EKG	X											
History & physical exam[A]	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[A]	X	X	X	X	X	X	X	X	X	X	X	
Performance Status	X											
CBC/Differential/Platelet count[B]	X	X	X	X	X	X	X	X	X	X	X	
ALT or AST, Total bilirubin, albumin, creatinine, uric acid, phosphorus, LDH[C]	X	X	X	X	X	X	X	X	X	X	X	
Bone Marrow & cytogenetics[D]	X (within 30days)	X		X								
Pregnancy test (If indicated)	X (within 7days)											
Echocardiogram or MUGA	X											
Chest X-ray	X											
Imaging Studies - Extramedullary Disease[E]	X											
Concomitant medication and AE assessment	X	X	X	X	X	X	X	X	X	X	X	X
Toxicity assessment		X	X	X	X	X	X	X	X	X	X	X

[A] Physical Exam and Vital Signs before start of cycles 1-9 and then before each tagraxofusp cycle during maintenance. Vitals signs including weight, respiration rate, pulse, and blood pressure.

[B] CBC, platelet count and differential: 1-2 weekly for cycle 1, then 1-3 weeks during intensive chemotherapy then every 4-8 weeks during maintenance. CBC, platelet count and differential should be checked prior to every dose of tagraxofusp.

[C] Total bilirubin, AST or ALT, albumin, creatinine, uric acid, phosphorus, LDH weekly during cycle 1, then every 1-3 weeks during intensive chemotherapy, then every 4-8 weeks during maintenance. Laboratory studies, including albumin, should be checked prior to every dose of tagraxofusp.

[D] Bone marrow for correlative samples should be performed prior to starting therapy. If unable to obtain a repeat bone marrow prior to study entry, most recent bone marrow should have been performed within 30 days of start of treatment. When possible, add cytogenetics, flow minimal residual disease assessment, and mutations. Additional bone marrow assessment after cycles 1 at C1D21 (± 7 days) and 3 at C3D28 (± 7 days), then at the end of every 1-3 cycles (± 7 days) during intensive chemotherapy and every 3-6 cycles (± 7 days) during maintenance, or as clinically indicated. Additional research samples for correlative studies will be performed at the end of cycle 1 bone marrow C1D21 (± 7 days) (i.e. after cycle of single-agent tagraxofusp) and at the time of relapsed. Patient who would have not yet achieved CR/CRi should have a bone marrow performed every cycle until response is documented or patient is removed from study

[E] Imaging studies (chest x-ray, CT chest, and/or PET scan) at the time of maximum response and/or when clinically determined to be necessary (in patients with extra-medullary disease at baseline only)

[F] Correlative peripheral blood samples will be collected anytime from the time of consent to prior the first dose of tagraxofusp (C1D1). All correlative samples (peripheral blood and bone marrow) will be sent to Dr. Kornblau's lab. Correlative samples will be performed as a batch at the end of the study and no data related to these samples will be captured in the case report form. Failure to obtain any correlative studies will not be considered a deviation.

6.1 Follow-up

Thirty days after last dose of the study drugs and AE assessment will be performed. This may be done over the phone with a member of the study staff. The phone call should last about 10 minutes. Patient will be contacted every 3 months (± 1 month) until patient death or patient is lost to follow-up.

7. EFFICACY AND SAFETY ASSESSMENTS

7.1. CRITERIA FOR RESPONSE

1. Complete Remission (CR): Normalization of the peripheral blood and bone marrow with 5% or less blasts in normocellular or hypercellular marrow with a granulocyte count of 1 x 10^9/L or above, and platelet count of 100 x 10^9/L. Complete resolution of all sites of extramedullary disease is required for CR.
2. Complete remission without recovery of counts (CRi): Peripheral blood and marrow results as for CR, but with incomplete recover of counts (platelets < 100 x 10^9/L; neutrophils < 1 x 10^9/L).
3. Partial Response (PR): As above for CR except for the presence of 6-25% marrow blasts.
4. Relapse and resistant disease will be defined based on morphological assessment of bone marrow and peripheral blood. Patients with new or recurrent CNS or extramedullary disease will also be considered to have relapsed disease.

7.2. EVALUATION OF TOXICITY

1. An adverse event (AE) is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. This includes the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug.

2. Toxicities will be graded according to the NCI Common Toxicity Criteria for Adverse Event Reporting Version 5 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). The toxicity of the regimen will be monitored continuously during the course of the study.

7.3. CRITERIA FOR REMOVAL FROM THE STUDY

1. Adverse events that are not manageable with dose adjustments and/or optimal medical management, or that, in the opinion of the investigator, pose an unacceptable risk for the patient
2. Non-compliance by the patient with protocol requirements
3. Failure to achieve CR, CRi or PR after at least 3 cycles, unless the patient has derived clinical benefit as defined by a reduction of transfusion requirements
4. Disease progression.
5. Patient death
6. Patient decision (e.g. withdrawal of consent)
7. Investigator decision, if it is deemed in the best interest of the patient

7.4 DEFINITION OF STUDY END-POINTS

1. **Relapse-free survival** is the time from documented complete response until relapse or death.

2. **Event-free survival** is the time from the first day of treatment until any failure (resistant disease, relapse, or death).

3. **Overall response rate** is defined as the percentage of patients achieving CR or CRi

4. **Overall survival** is defined as the time from the first day of treatment to time of death from any cause.

8. REPORTING REQUIREMENTS

8.1 Monitoring, Recording and Reporting Adverse Events

All consented subjects will be registered in the institutional database CORe.

Adverse event reporting will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled. For non-MD Anderson laboratory results, the principal investigator (or physician designee) will review laboratory results, and sign and date the results.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50).

Prometheus will be the electronic Case Report Form for adverse events. Baseline events will be recorded in the medical history section of the case report form (Prometheus) and will include the terminology event name, grade, and start date of the event. AEs will be recorded from the first dose through 30 days after the last dose. AEs will be shared with Astellas on an annual basis. Abnormal laboratory values or test results will not be recorded or reported as adverse events unless it leads to therapeutic intervention, results in dose modification or interruption, or meets the protocol definition of a DLT or SAE.

The Leukemia specific Adverse Event Recording and Reporting Guidelines will be followed for the recording and reporting of adverse event and serious adverse events on investigator-initiated trials within the Department of Leukemia.

1. Baseline events will be recorded in the medical history section of the case report form (CRF) and will include the diagnosis, grade, and start date of the event.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the first dose of study drug
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with any type of leukemia and/or related disorders.
    b. If exact start date is unknown, month and year or year may be used as the start date of the baseline event or “Unknown” may be recorded.
    c. The medical history section of the CRF will serve as the source document for baseline events once signed and dated by the Principal Investigator.
2. AEs will be captured starting from the first dose of the study drug to 30 days after the last dose of study drug or when the patient begins another treatment for the disease under study, whichever occurs first. Serious Adverse Events (SAEs) will be captured starting from the date of consent and reported according to institutional policy.
3. The maximum grade of the adverse event (AE) will be captured per course or protocol defined visit date. The start date will be recorded as when the AE first began or worsened from baseline, regardless of when the event was at its highest grade.
4. An AE will be recorded as intermittent if the AE is not continuous but reoccurs at an irregular interval within a course.
5. Only the following AEs from the Adverse Event Record will be reported in the CRF:
    a. Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
    b. All serious adverse events regardless of attribution to the study drug(s).
    c. Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.
6. Hematologic adverse events will not be recorded or reported for studies in patients with any type of leukemia and/or related disorders, except for:
    a. Prolonged myelosuppression as defined by marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts).
    b. Hematologic events that result in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
7. Other abnormal laboratory values, vital signs and test results constitute adverse events only if they lead to therapeutic intervention, discontinuation or delay in treatment, dose modification, or otherwise meet the criteria of a DLT or SAE. Lab abnormalities not meeting these criteria are considered not clinically significant.

8. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

8.2 Serious Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsored Single Site IND Protocols

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 event
- 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 on Reporting 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.

Procedures for Reporting Serious Adverse Events:

MDACC SAE form (eSAE) will be utilized for safety reporting to Stemline. SAEs will be reported to Stemline within timeframe per table 3, sec 8.3, of knowledge of any event via email: adverseevents@stemline.com.

8.3 Investigator Communications with Stemline

In addition to compliance with all FDA reporting requirements pursuant to 21 CFR 312, the Principal Investigator shall:

a) Report to Stemline serious adverse events (SAEs) experienced by a study subject receiving an Stemline product per the timelines and requirements in the table below. Principal Investigator shall make available to Stemline promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by Stemline, and,

Table 3: Investigator Communications

Deliverables	**Timeframe & Details**
IND Safety Report Notifications	Please notify Stemline of an upcoming submission to the IND. This notification would ideally include the following: • Timelines for IND Reporting • SAE Term(s) driving reportability
7-Day IND Safety Report	Send to Stemline as soon as it is ready, or within one (1) business day of completion of the eSAE Form. Please include: • Completed eSAE Form
15-Day IND Safety Report	Send to Stemline as soon as ready, but no later than five (5) business days of completion of the eSAE Form. Please include:

	• Completed eSAE Form
Fatal cases that are unrelated to Study Drug	Please send the completed eSAE form to Stemline within seven (7) business days. Follow-up information should also be provided within the same time frame.
Quarterly SAE Listings	On a quarterly basis, please provide SAE Line Listing from the study's safety database which includes: • Patient ID, Age and Gender • Study Drug start/stop dates • SAE Term • Event Onset Date • Severity Grade • Causality (Relationship to Study Drug) • Event Outcome

b) Notify Stemline upon any subjects receiving an Stemline Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

Stemline's contact for reporting serious adverse drug experiences, pregnancy experiences, and communications of FDA submissions of IND safety reports shall be adverseevents@stemline.com

Pregnancy related events will be submitted via eSAE application as "Other Important Medical Event".

Product Complaints: In addition to compliance with all FDA requirements pursuant to 21 CFR 211 and 21 CFR 820, Principal Investigator will report to Stemline within 24 hours any suspected quality defect in an Stemline Product or its Stemline-provided packaging, labeling, or medical device component (collectively, "Product Complaint"). Principal Investigator will report Product Complaints that involve an Stemline Product, whether Stemline has supplied the Stemline Product used in the Study or not. Stemline's contact for reporting Product Complaints shall be productcomplaints@stemline.com

9. OUTSIDE PHYSICIAN PARTICIPATION DURING TREATMENT

9.1. 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.

9.2. 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

9.3. 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 MDACC physician, indicating that they have reviewed it.

9.4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

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

9.6. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

9.7. Patients should receive all induction and consolidation at MDACC but may receive maintenance therapy by an outside physician. However, they will need to return to MDACC monthly during maintenance tagraxofusp cycles.

10. STATISTICAL METHODOLOGY

This is a single arm, open label, phase Ib/II study to assess the safety and efficacy of tagraxofusp plus low-intensity chemotherapy in patients with ALL.

Phase Ib

A safety lead-in design with 6 patients will be used to determine the MTD for the combination regimen. These patients will count toward the phase II part. If none or 1 out of the 6 patients experience a DLT, then the phase II will commence. If 2 or more patients experience a DLT, in which case the MTD has been exceeded, then a lower dose of the combination regimen could be assessed based on the investigators' decision, which will be implemented with amendment to the study.

Phase II

The primary endpoint of the phase II is overall response rate (ORR) of the combination regimen. A total 40 patients will be enrolled in the phase II part including the 6 patients of the phase Ib. The ORR and toxicity within 3 cycles of treatment initiation will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998). The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M D Anderson

Cancer Center was used to generate the stopping boundaries and operating characteristics for futility and toxicity monitoring. Toxicities are defined as grade 3/4/5 adverse events that are at least possibly related to study drug (with the exception of any adverse events that constitute exceptions to DLTs as above).

The historical ORR for ALL patients is 25%. It is expected for the current trial that the combination regimen will improve the ORR by 10%, while the toxicity rate is maintained at or below 20%. A sample size of 40 patients ensures that, if the trial is not terminated early, a posterior 95% credible interval for ORR will be (0.21, 0.49) under the assumption of a 35% of ORR and a prior of Beta (0.5, 1.5). The prior probabilities of ORR and toxicity for the experimental combination regimen are modeled by beta distributions Beta (0.5, 1.5) and Beta (0.4, 1.6), respectively. Denoting the historical proportion of overall response rate and toxicity rate by {p(ORR, H) = 0.25, p(TOX, H) = 0.20}, the following decision criteria will be applied:
1) Stop if Prob{$p(ORR, H) + \delta_{ORR} > p(ORR, E) \mid data$} > 0.975, where $\delta_{ORR} = 0$
2) Stop if Prob{$p(TOX, H) + \delta_{TOX} < p(TOX, E) \mid data$} > 0.80, where $\delta_{TOX} = 0$

Patients will be monitored in cohorts of 5 according to the following stopping boundaries for response and toxicity.

Table 4: Stopping Boundaries for Response and Toxicity

# Patients Evaluated	Stop this cohort if ≤ this # ORR	Stop if ≥ this # toxicities
5	Never stop with this many patients	3-5
10	0	4-10
15	0	5-15
20	0-1	6-20
25	0-2	7-25
30	0-3	9-30
35	0-4	10-35
40	Always stop with this many patients	Always stop with this many patients

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

Table 5: Operating Characteristics

True Toxicity Rate	True ORR	Prob(Stop Early)
0.10	0.25	0.1287
	0.30	0.0704
	0.35	0.0468
	0.40	0.0373
	0.45	0.0334
0.20	0.25	0.3967
	0.30	0.3564

	0.35	0.3400
	0.40	0.3334
	0.45	0.3307
0.30	0.25	0.8005
	0.30	0.7872
	0.35	0.7817
	0.40	0.7796
	0.45	0.7787
0.40	0.25	0.9736
	0.30	0.9719
	0.35	0.9711
	0.40	0.9709
	0.45	0.9707
0.50	0.25	0.9988
	0.30	0.9987
	0.35	0.9987
	0.40	0.9986
	0.45	0.9986

Statistical Analysis Plan

All patients who received at least one dose of study drug will be included in the intent-to-treat analysis for efficacy and safety. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency using frequency tables. Demographic/clinical characteristics (such as duration of response) will be summarized using descriptive statistics such as mean, standard deviation, median and range. Overall response rate, and CR rate within 3 cycles of treatment initiation will be estimated along with 95% credible intervals. Chi-square tests or Fisher's exact test will be used to evaluate the association between patient's prognostic factor and response. Kaplan-Meier method will be used to estimate the relapsed-free survival (RFS), and overall survival. RFS is defined as the time from the of response to relapsed or death, whichever happens earlier. It will be censored at last follow-up. Paired t-tests will be used to determine the gene expressions and other clinical variables changes from pre-therapy to the predefined time-points.

The Investigator is responsible for completing an efficacy/safety summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval

- Lead-In Phase:

After the first 3 evaluable patients, complete 3 cycles of study treatment, and every 3 evaluable patients complete 3 cycles thereafter, IND Office approval must be obtained prior to expanding/changing dose levels.

- Phase II:

After the first 5 evaluable patients complete 3 cycles of study treatment, and every 5 patients complete 3 cycles of treatment thereafter.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

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Appendix A: Updated Tagroxfusp (SL-401) Capillary Leak Syndrome (CLS) Management and Guidelines.

Dose Delays/Modifications and Management Procedures for Toxicities Associated with tagraxofusp

During the dosing period for each cycle, individual tagroxofusp infusions may be delayed to allow for toxicity resolution. Details are presented in the Table A-1 below:

Monitor vital signs/weight and check albumin, transaminases, and creatinine prior to preparing each dose of tagraxofusp. See Table below for CLS management guidance.

Table A-1 Recommended Tagraxofusp Dose Modifications

Parameter	Severity Criteria	Dose Modification
Serum albumin	Serum albumin < 3.5 g/dL or reduced ≥ 0.5 g/dL from value measured prior to initiation of the current cycle	See CLS Management Guidelines (Table A-2)
Body weight	Body weight increase ≥ 1.5 kg over pretreatment weight on prior treatment day	See CLS Management Guidelines (Table A-2)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	ALT or AST increase > 5 times the upper limit of normal	Withhold tagraxofusp until transaminase elevations are ≤ 2.5 times the upper limit of normal.
Serum creatinine	Serum creatinine > 1.8 mg/dL (159 micromol/L) or creatinine clearance < 60 mL/minute	Withhold tagraxofusp until serum creatinine resolves to ≤ 1.8 mg/dL (159 micromol/L) or creatinine clearance ≥ 60 mL/minute.
Systolic blood pressure	Systolic blood pressure ≥ 160 mmHg or ≤ 80 mmHg	Withhold tagraxofusp until systolic blood pressure is < 160 mmHg or > 80 mmHg.
Heart rate	Heart rate ≥ 130 bpm or ≤ 40 bpm	Withhold tagraxofusp until heart rate is < 130 bpm or > 40 bpm.
Body temperature	Body temperature ≥ 38°C	Withhold SL-401 until body temperature is < 38°C.
Hypersensitivity reactions	Mild or moderate	Withhold tagraxofusp until resolution of any mild or moderate hypersensitivity reaction. Resume SL-401 at the same infusion rate.
	Severe or life-threatening	Discontinue tagraxofusp permanently.

Dose reductions should be discussed with the medical monitor or PI on a case by case basis.

Table A-2: CLS Management Guidance

<table>
<tr><th>Time of Presentation</th><th>CLS Sign/Symptom</th><th>Recommended Action</th><th>SL-401 Dosing Management</th></tr>
<tr><td>Prior to first dose of SL-401 in Cycle 1</td><td>Serum albumin < 3.2 g/dL</td><td colspan="2">Administer SL-401 when serum albumin ≥ 3.2 g/dL.</td></tr>
<tr><td rowspan="4">During SL-401 dosing</td><td>Serum albumin < 3.5 g/dL</td><td rowspan="2">Administer 25g intravenous albumin (q12h or more frequently as practical) until serum albumin is ≥ 3.5 g/dL AND not more than 0.5 g/dL lower than the value measured prior to dosing initiation of the current cycle.</td><td rowspan="3">Interrupt SL-401 dosing until the relevant CLS sign/symptom has resolved[1].</td></tr>
<tr><td>Serum albumin reduced by ≥ 0.5 g/dL from the albumin value measured prior to SL-401 dosing initiation of the current cycle</td></tr>
<tr><td>A predose body weight that is increased by ≥ 1.5 kg over the previous day’s predose weight</td><td>Administer 25g intravenous albumin (q12h or more frequently as practical), and manage fluid status as indicated clinically (e.g., generally with intravenous fluids and vasopressors if hypotensive and with diuretics if normotensive or hypertensive), until body weight increase has resolved (i.e. the increase is no longer ≥ 1.5 kg greater than the previous day’s predose weight).</td></tr>
<tr><td>Edema, fluid overload and/or hypotension</td><td>Administer 25g intravenous albumin (q12h, or more frequently as practical) until serum albumin is ≥ 3.5 g/dL.

Administer 1 mg/kg of methylprednisolone (or an equivalent) per day, until resolution of CLS sign/symptom or as indicated clinically.

Aggressive management of fluid status and hypotension if present, which could include intravenous fluids and/or diuretics or other blood pressure management, until resolution of CLS sign/symptom or as clinically indicated.</td></tr>
</table>

[1] SL-401 administration may resume in the same cycle if all CLS signs/symptoms have resolved and the patient did not require measures to treat hemodynamic instability. SL-401 administration should be held for the remainder of the cycle if CLS signs/symptoms have not resolved or the patient required measures to treat hemodynamic instability (e.g. required administration of intravenous fluids and/or vasopressors to treat hypotension) (even if resolved), and SL-401 administration may only resume in the next cycle if all CLS signs/symptoms have resolved, and the patient is hemodynamically stable.

Appendix B

Correlative plan for genomic profiling of ALL cases.

Background and objectives:

Acute lymphoblastic leukemia (ALL) is a highly heterogeneous disease driven by various genetic lesions[1]. Recent years, with the effort of large scale transcriptome sequencing (RNA-seq) of ALL, multiple novel subtypes had been identified by analyzing the distinct gene expression profile and the causal genetic lesions[2-9]. RNA-seq has been shown with high reliability of evaluating the gene expression profile and high sensitivity of identifying the driver genetic lesions including gene rearrangements, large scale copy number alterations, and even sequence mutations, which position RNA-seq as an ideal platform to assist the molecular diagnosis and profiling of ALL[10,11]. Based on our previous research[8,10], here we will apply an RNA-seq based analysis pipeline to study the gene expression profile and genetic lesions of the enrolled ALL cases to achieve the following **Specific Aims**:

1. Classify the leukemic samples (collected at pre- and post- tagraxofusp treatment) into different ALL subtypes according to the driver genetic lesions and gene expression profiles
2. Identify drug response relevant gene sets and biological pathways through differential gene expression analysis between good vs poor responders
3. Validate the connection of reported *CD123* and *DPH1* (encoding a diphthamide pathway enzyme) expression levels[12] and drug responses in ALL
4. Identify clonal evolution and key genetic lesions introduced through tagraxofusp treatment from diagnosis to relapse through RNA-seq and whole genome sequencing (WGS).

Materials and research approaches:
For diagnosis and relapsed samples, at least 5 million blast cells are required to perform genomic profiling (RNA-seq for all the leukemic samples; WGS for ALL missing driver genetic lesion by RNA-seq or for mutational spectrum analysis), genetic alteration validation, and following functional characterization of leukemic cells. For samples with low blast percentage (<70%), which is common in relapsed cases, the leukemic cells will be enriched through fluorescence-activated cell sorting (FACS) or magnetic beads enrichment before extracting DNA and RNA for sequencing. With 2-3 million cells, at least 1μg RNA can be extracted and submitted for RNA-seq. The rest amount of RNA will be secured for validating the genetic lesions identified by RNA-seq through RT-PCR and sanger sequencing. Although most of ALL cases can be classified into distinct subtypes using RNA-seq[10], around 5~10% are missing driver lesions, thus WGS (≥1μg DNA, from 1-2 million cells) of tumor and matched germline samples will be used to further assist the disease classification. To minimize the patient sample requirement, the RNA/DNA extraction and sequencing library preparation will be carefully carried out within Dr. Gu's laboratory at City of Hope by a senior lab member through consistent sample processing pipelines and protocols, then the libraries will be submitted for Illumina high-throughput sequencing. To achieve sufficient sensitivity and accuracy of calling fusions and detect genetic lesions from RNA-seq, 50 million 2X150bp reads will be generated. For WGS, 500 million 2X150bp reads are required for each sample.

Specific Aim 1: The RNA-seq data will be analyzed to call gene rearrangements (e.g. *BCR-ABL1*), gene expression profiles, digital karyotypes[10], key sequence mutations (e.g., *NRAS*, *KRAS*, *PAX5*, *IL7R*, etc.), and key intragenic copy number alterations (e.g., *IKZF1*, *ERG*, *PAX5*, etc.). The genetic and transcriptomic information will be integrated to assign ALL samples into distinct disease subtypes[7,10,13]. Should there be a small number of ALL cases fail the RNA-seq based disease classification, WGS will be applied to call sequencing mutations, granular copy number alterations, and large-scale structure variations, and the results will be integrated with RNA-seq to clarify the genetic background of these cases.

Specific Aim 2: From RNA-seq, the gene expression level will be evaluated and normalized for the enrolled ALL cohort to identify differentially expressed genes between good and poor tagraxofusp responders. Gene set enrichment and pathway analysis will be performed to identify signature genes and biological pathways which can potentially explain and/or predict drug response. With the promising candidate genes and pathways identified, patient-derived xenograft mouse models could be used to verify the results.

Specific Aim 3: Tagraxofusp is a CD123-targeted agent, but the factors influencing the response other than *CD123* expression are largely unknown. A study from Togami *et al*.[12] showed that expression of *DPH1*, which encodes a diphthamide pathway enzyme, was reduced by DNA CpG methylation in resistant acute myeloid leukemia and blastic plasmacytoid dendritic cell neoplasm. With the whole transcriptome information acquired from RNA-seq, the connection between drug resistance and expression level of *CD123*/*DPH1* will be specifically assessed in the context of ALL.

Specific Aim 4: For the ALL cases with both diagnosis and relapsed samples available, WGS will be complemented to RNA-seq to call genetic alterations including sequencing mutation, copy number alteration and structure variation. The progression of genetic lesions and gene expression profiles from diagnosis to release will be characterized to identify the genetic lesions and deregulated gene expression pathways introduced by the selective pressure from tagraxofusp treatment, which will bring insights of developing synergistic regimens to further dwindle the risk of relapse.
In summary, through the proposed genomic profiling of ALL cases enrolled in the tagraxofusp clinical trial, the genomic and transcriptomic background of each patient will be thoroughly characterized, which will facilitate the interpretation of the treatment response, identify molecular markers to stratify the risk groups, and inspire the development of combined treatments to advance the efficacy of tagraxofusp in curing ALL.

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