COG-AALL2121: A Phase 2 study of SNDX-5613 in combination with chemotherapy for patients with relapsed or refractory KMT2A-rearranged infant leukemia

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

PATIENT ELIGIBILITY:
Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

Laboratory Studies
All laboratory studies to determine eligibility must be performed within 7 days prior to *enrollment* unless otherwise indicated.

The following laboratory studies must be repeated prior to the *start of protocol therapy: CBC with differential, electrolytes (specifically potassium and magnesium) in order to ensure labs continue to meet parameters* appropriate for SNDX-5613 dosing, see Section 4.6.3 and Section 4.9.3). The following laboratory studies must be repeated prior to the start of protocol therapy only if > 7 days have elapsed from their most recent prior assessment: bilirubin, ALT (SGPT) and serum creatinine. Laboratory tests for these specific labs need not be repeated if therapy starts within seven (7) days of their most recent prior assessment.

If the result of a laboratory study that is repeated at any time *post-enrollment* and prior to the *start of protocol therapy* is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to initiating protocol therapy. The results of the recheck must be within the limits for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Clinical Studies
Clinical studies (e.g., cardiac imaging, pulmonary function tests), if applicable, must be obtained within 21 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

Disease/Staging Imaging
Disease/staging bone marrow assessment and imaging studies, if applicable, must be obtained within 21 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

___1. Reservation Requirement: Prior to obtaining informed consent and enrolling a patient, a reservation must be made. See Section 3.1.3.

___2. Timing
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.**

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

___3. Callback for Dose Level Assignment
For patients receiving Regimen A, there will be a callback following disease evaluations post-Cycle 1 to confirm dose level for Cycle 2 (or, for specific patients, at the determination of meeting Early Progressive Disease criteria, see Section 10.2.4). This is necessary because safety/toxicity evaluations for patients receiving Regimen B inform the dosing decision for patients receiving Regimen A Cycle 2. Patients that do not correctly complete callback at the following timepoint will be deemed a protocol deviation and be taken off protocol.

Callback	Timing	Population	Purpose
Regimen A post-Cycle 1 Callback	Post-Cycle 1 disease evaluation (or at determination of Early Progressive Disease)	Patients receiving Regimen A and either completed Cycle 1 or met criteria for Early Progressive Disease	Dose level determination for Regimen A Cycle 2

___4. Age: Patients must be 1 month to < 6 years old at the time of study enrollment and must have had initial diagnosis of leukemia at < 2 years old.

___5. Diagnosis

- Patients must have *KMT2A*-rearranged acute lymphoblastic leukemia (ALL), acute leukemia of ambiguous lineage (ALAL), or mixed phenotype acute leukemia (MPAL), which is determined to be refractory or in first marrow relapse (defined below in Section 3.2.2.2). Patients who have experienced lineage switch to acute myeloid leukemia (AML) are eligible assuming documented prior diagnosis of *KMT2A*-rearranged ALL/ALAL/MPAL.

  All patients must undergo cytogenetics and FISH testing of a relapsed/refractory blast sample at a COG-approved laboratory for *KMT2A*-R status determination and the presence of a *KMT2A*- rearrangement must be confirmed by central review. Cytogenetics results must be submitted for central review by Day 10 of protocol therapy, for confirmation of *KMT2A*-R status. Patients enrolled with refractory disease may utilize initial diagnostic cytogenetics for eligibility and submission for central review if testing was performed at a COG approved laboratory. Patients will be eligible to remain on protocol therapy if *KMT2A*-R is confirmed by central review. Additional methods of assessing for *KMT2A*-R may be considered if FISH does not detect the rearrangement. Please refer to Section 14.6 for sample details regarding central review.

- Disease status at time of enrollment must be one of the following:
  a. First relapse: Any recurrence of marrow disease, with or without other extramedullary sites(s), at any point after achieving remission. ("Remission-1", per definition below) meeting one of these criteria: (See Section 3.3.2)
     i. Relapse M1: M1 morphology (< 5% blasts) + at least 2 confirmatory tests showing ≥ 1% blasts (testing includes flow, cytogenetics, PCR/NGS of Ig/TCR rearrangement, and/or PCR or NGS of fusion gene identical to diagnosis), OR
     ii. Relapse M2: M2 morphology (5-25% blasts) + 1 confirmatory test showing > 1% blasts, OR
     iii. Relapse M3: M3 morphology (> 25% blasts)
  b. Refractory, or failure to achieve Remission-1: Remission-1 is defined as < 1% marrow blasts by flow MRD and resolution of extramedullary disease by the end of Consolidation, or 2 courses of frontline chemotherapy.
  c. CNS disease: Patients must have CNS1 or CNS2 status (see Section 3.3.1) and no clinical signs or neurologic symptoms suggestive of CNS leukemia, such as cranial palsy.
     i. Patients with CNS3 disease may receive antecedent intrathecal chemotherapy to achieve CNS1 or CNS2 status prior to enrollment.
     ii. Patients with a history of CNS chloromatous disease are required to have no radiographic evidence of CNS disease prior to enrollment.
  d. White blood cell (WBC) must be < 50,000/μL at the time of study enrollment. Patients can receive cytoreduction with hydroxyurea and/or corticosteroids for up to 7 days prior to enrollment (See Section 3.2.4.1).

___6. Performance Level
Patients ≥ 12 months of age must have a performance status by Lansky Scale of ≥ 50% (See Appendix II).

___7. Patients must be able to take enteral medications. Acceptable routes of administration for SNDX-5613 include: oral (PO), nasogastric (NG) tube, nasojejunal (NJ) tube, nasoduodenal (ND), and gastrostomy tube (G-tube).

___8. Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

- Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive: See DVL homepage for commercial and Phase 1 investigational agent classifications (https://cogmembers.org/uploadedFiles/Site/Disc/DVL/Documents/TableOfMyelosuppressiveAnti-CancerAgents.pdf). For agents not listed, the duration of this interval must be discussed with the Study Chair and study-assigned Research Coordinator prior to enrollment.

  ≥ 14 days must have elapsed after the completion of other cytotoxic therapy, including patients who relapse during pre-Maintenance upfront therapy, with these specific exceptions: cytoreduction with hydroxyurea and/or corticosteroids, and intrathecal chemotherapy, which have no required washout periods (see below). For patients who relapse during upfront Maintenance therapy, ≥ 7 days must have elapsed after the last dose of chemotherapy. Additionally, patients must have fully recovered from all acute toxic effects of prior therapy.

  NOTE: Cytoreduction with hydroxyurea and/or corticosteroids is permitted prior to enrollment for patients with WBC ≥ 50,000/μL, and by provider discretion regardless of WBC, to reduce potential risk of differentiation syndrome with SNDX-5613 initiation. Hydroxyurea and/or corticosteroids may be given for up to 7 days, with no wash-out required.

  NOTE: No waiting period is required for patients having received intrathecal cytarabine, methotrexate, and/or hydrocortisone. Intrathecal chemotherapy that is given up to 7 days prior to the initiation of protocol therapy counts as protocol therapy and not prior anti-cancer therapy. Intrathecal chemotherapy given > 7 days prior does not count as protocol therapy.

  NOTE: Prior exposure to fludarabine and cytarabine (FLA) is permitted.

- Anti-cancer agents not known to be myelosuppressive (e.g., not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See DVL homepage for commercial and Phase 1 investigational agent classifications (https://cogmembers.org/uploadedFiles/Site/Disc/DVL/Documents/TableOfMyelosuppressiveAnti-CancerAgents.pdf). For agents not listed, the duration of this interval must be discussed with the study chair and study-assigned Research Coordinator prior to enrollment.

- Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1. There is an exception for blinatumomab infusions, for which patients must have been off for at least 3 days and all drug related toxicity must have resolved to Grade 2 or lower as outlined in the inclusion/exclusion criteria.

- Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g., pegfilgrastim) or ≥ 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator.

- Interleukins, Interferons and Cytokines (other than hematopoietic growth factors): ≥ 21 days after the completion of interleukins, interferon, or cytokines

- Stem cell infusions (with or without TBI):
  i. Allogeneic (non-autologous) bone marrow or stem cell transplant, or stem cell boost: ≥ 84 days after infusion
  ii. Donor leukocyte infusion: ≥ 28 days

- Cellular Therapy: ≥ 28 days after the completion of any type of cellular therapy (e.g., modified T cells, NK cells, dendritic cells, etc.)

- XRT/External Beam Irradiation including protons: ≥ 14 days after local XRT; ≥ 84 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial bone marrow radiation.

___9. Organ Function Requirements

- Adequate Renal Function Defined As:
  A serum creatinine based on age as follows:

Age	Maximum Serum Creatinine (mg/dL)
1 month to < 6 months	0.4
6 months to < 1 year	0.5
1 to < 2 years	0.6
2 to < 6 years	0.8

  The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.

  OR - a 24-hour urine Creatinine clearance ≥ 70 mL/min/1.73 m^2

  OR - a GFR ≥ 70 mL/min/1.73 m^2. GFR must be performed using direct measurement with a nuclear blood sampling method OR direct small molecule clearance method (iothalamate or other molecule per institutional standard).

  NOTE: Estimated GFR (eGFR) from serum creatinine, cystatin C or other estimates are not acceptable for determining eligibility.

- Adequate Liver Function Defined As:
  - A direct bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, unless disease related, AND
  - SGPT (ALT) ≤ 135 U/L* (3 x ULN) unless disease related.

  Note: For the purpose of eligibility, the ULN for SGPT (ALT) has been set to the value of 45 U/L

- Adequate Cardiac Function Defined As:
  - Shortening fraction of ≥ 27% by echocardiogram, or
  - Ejection fraction of ≥ 50% by radionuclide angiogram.
    AND
  - Corrected QT interval using Fridericia formula (QTcF) of < 450 msec (using the average of triplicate measurements)

- **NOTE:** There are no specific electrolyte parameters for eligibility. However, it should be noted that, to limit QTc prolongation risk, patients must maintain adequate potassium and magnesium levels to initiate and continue SNDX-5613 on protocol therapy. (See Section 4.6.3 and Section 4.8.3 for Cycle 1 requirements).

___10. Patients must be able to comply with the safety monitoring requirements of the study, in the opinion of the treating investigator.

___11. Central Review of Cytogenetics/FISH is required. Also see section 14.6.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix IX.

EXCLUSION CRITERIA

___1. Patients with isolated extramedullary leukemia.

___2. Patients diagnosed with Down syndrome.

___3. Patients known to have one of the following syndromes:
Bloom syndrome, ataxia-telangiectasia, Fanconi anemia, Kostmann syndrome, Schwachman syndrome, or any other known bone marrow failure syndrome.

___4. Patients with a secondary *KMT2A*-R leukemia that developed after treatment of prior malignancy with cytotoxic chemotherapy.

___5. Patients with a history of congenital prolonged QT syndrome, congestive heart failure or uncontrolled arrythmia in the past 6 months prior to study enrollment.

___6. Patients with an active, uncontrolled infection, further defined below:
- Positive bacterial blood culture within 48 hours of study enrollment
- Fever above 38.2° C within 48 hours of study enrollment with clinical signs of infection. Fever that is determined to be due to tumor burden is allowed if patients have documented negative blood cultures for at least 48 hours prior to enrollment and no concurrent signs or symptoms of active infection or hemodynamic instability
- A positive fungal culture within 30 days of study enrollment or active therapy for presumed invasive fungal infection
- Patients may be receiving IV or oral antibiotics to complete a course of therapy for a prior documented infection as long as cultures have been negative for at least 48 hours and signs or symptoms of active infection have resolved. For patients with *C.difficile* diarrhea, at least 72 hours of antibacterial therapy must have elapsed and stools must have normalized to baseline
- Active viral or protozoal infection requiring IV treatment
- HIV-infected patients are eligible if on effective anti-retroviral therapy that does not interact with planned study agents and with undetectable viral load within 6 months of enrollment

___7. Patients with active acute graft-versus-host disease (GVHD) > Grade 0 (unless skin only), or chronic GVHD > mild (unless skin only) are not eligible. Patients with acute or chronic skin GVHD that is ≤ Grade 1, or chronic skin GVHD that is graded as mild are eligible. See Appendix XI for grading.

___8. Patients who have received a prior solid organ transplantation.

___9. Patients with known Charcot-Marie-Tooth disease, if treating on Regimen A (with vincristine).

___10. Concomitant Medications
- CYP3A4 Inhibitors or Inducers: Patients who require concomitant therapy with moderate or strong CYP3A4 inhibitors or inducers, as these are prohibited during the chemotherapy combination cycles. These agents should be discontinued at least 5 half-lives prior to starting protocol therapy. Concomitant use of strong CYP3A4 inhibitor -azole antifungals are permitted during the SNDX-5613 monotherapy cycles, with appropriate SNDX-5613 dose modification (see Section 4.1 and Section 4.5.5.2). See Appendix IV for a list of agents.
- P-glycoprotein (P-gp) inhibitors or inducers: Vincristine is a substrate for P-gp. Concomitant use of P-gp inhibitors or inducers with vincristine (patients receiving Regimen A Cycle 1) should be avoided. See Appendix VI for a list of P-gp inhibitors and inducers.
- Investigational Drugs: Patients who are currently receiving another investigational drug.
- Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents (exceptions: hydroxyurea and corticosteroids, which may be used as cytoreduction prior to enrollment, see Section 3.2.4.1).
- Anti-GVHD Agents: Patients who are receiving cyclosporine, tacrolimus, or other systemic agents to treat graft-versus-host disease post bone marrow transplant. Patients should discontinue anti-GVHD agents > 7 days prior to enrollment and have no evidence of worsening GVHD. Topical steroids are permitted.

___11. Patients who have previously been treated with SNDX-5613. Prior exposure to other menin inhibitors is permitted.

REQUIRED OBSERVATIONS:

Required Observations in Regimen A Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical exam
b. Height, weight, BSA
c. Vital Signs
d. Performance Status
e. CBC, differential, and platelets
f. Electrolytes including Ca++, Mg++, PO4, BUN and creatinine (recommend obtaining at least once daily during days 1-4 to monitor for tumor lysis syndrome; increase frequency or prolong duration as needed with any evidence of tumor lysis syndrome)
g. Uric acid (recommend obtaining at least once daily during days 1-4 to monitor for tumor lysis syndrome; increase frequency or prolong duration as needed with any evidence of tumor lysis syndrome)
h. AST, ALT, and total bilirubin
i. Endocrine panel: PTH, prolactin, TSH, free T4, insulin-like growth factor 1, LH, FSH, estradiol (females) or testosterone (males)
j. 12-lead ECG, each timepoint performed in triplicate. Pre-dose (within 6 hours) and 2 Hr post-dose (+/- 30 min). Obtain a 4 Hr post-dose (+/- 30 min) if prolonged QTc ≥ 450 ms on 2 Hr post-dose.
k. MUGA or ECHO
l. Ophthalmologic exam (baseline to be performed within 7 days preceding Day 1 treatment): visual acuity, slit lamp (as tolerated by patient age)
m. Obtain with each IT administration: CSF cell count, differential and cytospin
n. Bone marrow evaluation. BM evaluation at study entry should include morphology, immunophenotyping & cytogenetics/FISH. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab. (https://www.cogmembers.org/uploadedFiles/Site/Admin/Uploaded_Documents/Cytogenetics_Approved_Labs.pdf) and sent for central confirmation (Section 14.6).
o. Bone marrow evaluation for local morphology and for MRD by central flow cytometry (Section 14.1). Must be performed on Day 29 (See Section 4.3.1).
p. Evaluation of testicular and extramedullary disease, if applicable. (See Section 4.3.2 and Section 4.3.3).
q. Medication diary. See Appendix VII.
r. SNDX-5613 Pharmacokinetic Studies (Required in Safety Phase, Optional in Expansion Phase): See Section 14.3
s. Calaspargase pegol-mknl Pharmacokinetic Studies (Optional): See Section 14.4. For consented patients who receive Calaspargase pegol-mknl and then meet Early Progressive Disease criteria, obtain samples at same post-infusion timepoints despite patient proceeding to Regimen A Cycle 2.
t. Pharmacodynamic Studies (Optional): See Section 14.5

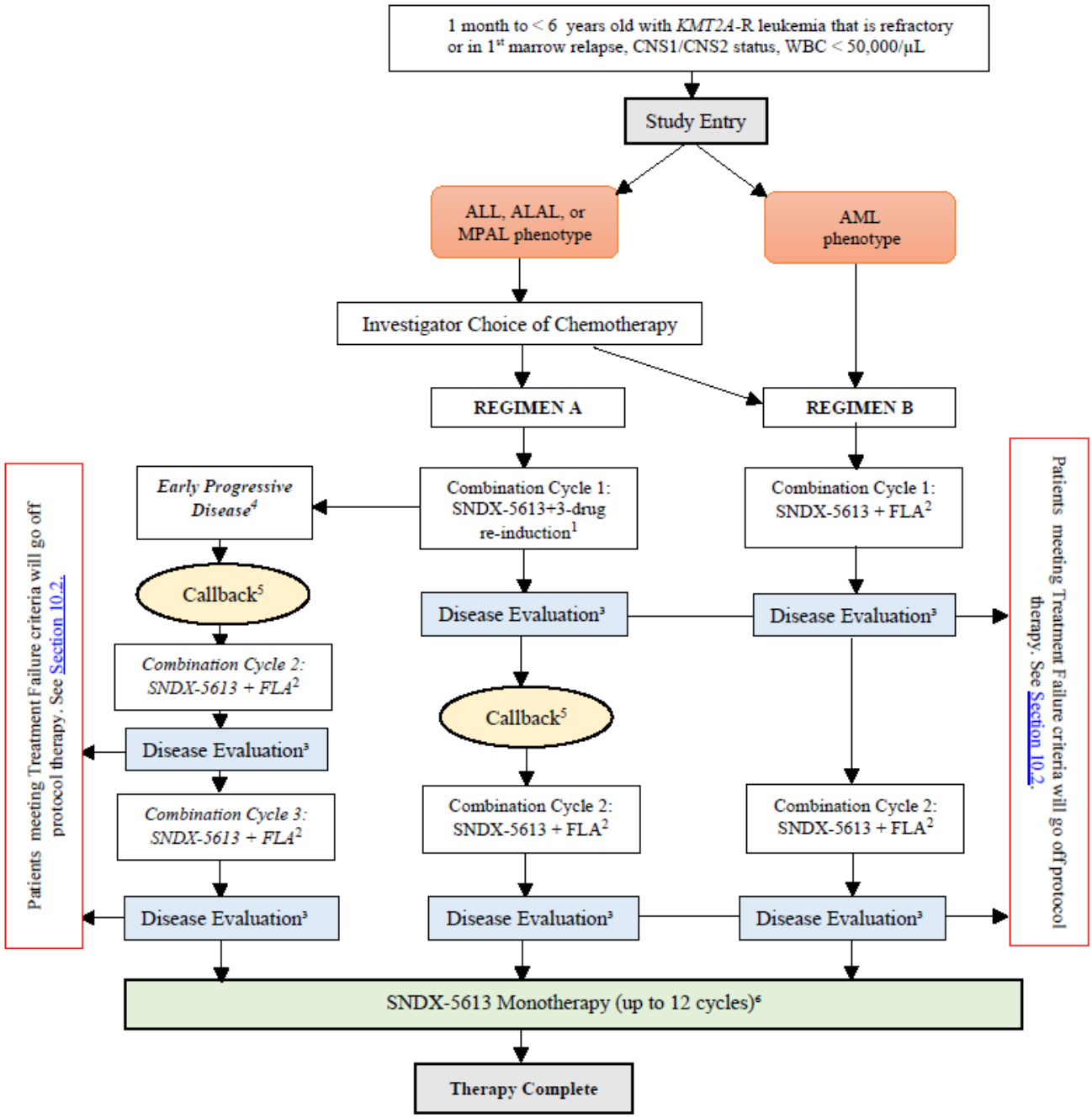
Required Observations in Regimen B Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical exam
b. Height, weight, BSA
c. Vital Signs
d. Performance Status
e. CBC, differential, and platelets
f. Electrolytes including Ca++, Mg++, PO4, BUN and creatinine (recommend obtaining at least once daily during days 1-4 to monitor for tumor lysis syndrome; increase frequency or prolong duration as needed with any evidence of tumor lysis syndrome)
g. Uric acid (recommend obtaining at least once daily during days 1-4 to monitor for tumor lysis syndrome; increase frequency or prolong duration as needed with any evidence of tumor lysis syndrome)
h. AST, ALT, and total bilirubin
i. Endocrine panel: PTH, prolactin, TSH, free T4, insulin-like growth factor 1, LH, FSH, estradiol (females) or testosterone (males)
j. 12-lead ECG, each timepoint performed in triplicate. Pre-dose (within 6 hours) and 2 Hr post-dose (+/- 30 min). Obtain a 4 Hr post-dose (+/- 30 min) if prolonged QTc ≥ 450 ms on 2 Hr post-dose.
k. MUGA or ECHO
l. Ophthalmologic exam (baseline to be performed within 7 days preceding Day 1 treatment): visual acuity, slit lamp (as tolerated by patient age)
m. Obtain with each IT administration: CSF cell count, differential and cytospin
n. Bone marrow evaluation. BM evaluation at study entry should include morphology, immunophenotyping & cytogenetics/FISH. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab. (https://www.cogmembers.org/uploadedFiles/Site/Admin/Uploaded_Documents/Cytogenetics_Approved_Labs.pdf) and sent for central confirmation (See Section 14.5)
o. Bone marrow evaluation for local morphology and for MRD by central flow cytometry (Section 14.1). Obtain between Day 29-35 depending on count recovery (See Section 4.3.1).
p. Evaluation of testicular and extramedullary disease, if applicable. See Section 4.3.2 and Section 4.3.3.
q. Medication diary. See Appendix VII.
r. SNDX-5613 Pharmacokinetic Studies (Required in Safety Phase, Optional in Expansion Phase): See Section 14.3.
s. Pharmacodynamic Studies (Optional): See Section 14.5.

TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA



[1]3-drug re-induction: prednisone, vincristine, asparaginase
[2]FLA: fludarabine and cytarabine
[3]Patients not meeting Treatment Failure criteria may continue on protocol therapy, see Section 10.2.
[4]For Early Progressive Disease definition, see Section 10.2.4.
[5]Callback for dose level assignment for Regimen A Cycle 2 only, see Section 3.1.6.
[6]Patients must maintain M1 marrow without meeting Rel-M1 criteria to continue with additional Monotherapy cycles (see Section 4.11.4).

ALL: Acute lymphoblastic leukemia
ALAL: Acute leukemia of ambiguous lineage
MPAL: Mixed phenotype acute leukemia
AML: Acute myeloid leukemia
WBC: White blood cell

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

SPECIMEN REQUIREMENTS:
Sampling Schedule

- Screening/Baseline
- End of Combination Cycle 1
- End of Combination Cycle 2
- End of Combination Cycle 3 (if applicable, only for patients with Early Progressive Disease in Regimen A Cycle 1)

Also see Section 14.2 for MRD schedule.

Also see Section 14.3 for required PK during Safety Phase.

Also see Section 14.4 for OPTIONAL Calaspargase PK for Regimen A.

Also see Section 14.5 for OPTIONAL Pharmacodynamics**.**