PROTOCOL TITLE:

A Pilot Study of Targeted Daunorubicin Dosing to Overcome Chemotherapeutic Resistance in Children with Relapsed or Refractory Acute Leukemia

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1.0 Study Summary

Study Title	A Pilot Study of Targeted Daunorubicin Dosing to Overcome Chemotherapeutic Resistance in Children with Relapsed or Refractory Acute Leukemia
Study Design	prospective, upfront window
Primary Objective	1To assess the feasibility and tolerability of administration of low dose daunorubicin 2 To observe if T-cell based immune responses against chemoresistant leukemia stem cells (LSC) are stimulated at lower doses of daunorubicin to provide preliminary data for further research. 3 To identify the pro- vs. anti-cancer cellular immune response of targeted anthracycline treatment in patients with relapsed/refractory AML.
Secondary Objective(s)	To evaluate the pharmacokinetic parameters of low dose daunorubicin in children with relapsed/refractory AML and ALL as well as standard doses of daunorubicin in children with AML and ALL to assess for dose linearity relationship
Research Intervention(s)/ Investigational Agent(s)	Daunorubicin at 6.75mg/m^2/day given IV days 1-5 as an upfront window therapy
IND/IDE #	NA
Study Population	ALL and AML refractory to two induction attempts, or 2nd or greater relapse, or in 1st relapse who are unable to receive standard intensive therapy PK analysis will also include first diagnosis ALL and AML who are receiving daunorubicin as standard of care
Sample Size	10 to receive low dose dauno; 5 of whom will not have had a SCT 12 additional patients for PK analysis
Study Duration for Individual Participants	5 days of treatment with 60 days of follow-up for patients receiving low dose daunorubicin
Study Specific Abbreviations/ Definitions	ALL – acute lymphoid leukemia; AML – acute myeloid leukemia, SCT – stem cell transplant; DNR daunorubicin

2.0 Objectives

2.1 Primary Objectives

2.1.1 To assess the feasibility and tolerability of administration of low dose daunorubicin

2.1.2 To observe if T-cell based immune responses against chemoresistant leukemia stem cells (LSC) are stimulated at lower doses of daunorubicin to provide preliminary data for further research.

2.1.3 To identify the pro- vs. anti-cancer cellular immune response of targeted anthracycline treatment in patients with relapsed/refractory AML.

2.2 Secondary Objective

2.2.1 To evaluate the pharmacokinetic parameters of low dose daunorubicin in children with relapsed/refractory AML and ALL as well as standard doses of daunorubicin in children with AML and ALL to assess for dose linearity relationship.

3.0 Background

3.1 Over the past 60 years there has been remarkable progress in our understanding of how to successfully use chemotherapy to treat children with cancer. Despite this progress and resultant cure rate of approximately 80%, cancer remains the number one cause of non-accidental death in children.[1-2] Many of these deaths are due to relapsed disease with survival rates ranging from 15-50% while those experiencing early relapse (within 18 months of diagnosis) have a 5-year survival estimate of only 20%. [3-4]

Leukemia is the most common type of childhood cancer. Chemoresistant leukemia stem cells (LSCs) are responsible for cancer treatment failure, but targeting these cells remains a significant challenge. Recent data indicates that certain cancer therapies act, in part, by reactivating anti-cancer immunity whereas other therapies may be immunosuppressive.

3.2 It is well established that the Wnt/β-catenin and PI3K/Akt pathways, which are frequently activated in human cancer, interact to drive LSC development and chemoresistance. [11-12] Prior investigations by Dr. John Perry unexpectedly found that doxorubicin (DXR) and daunorubicin (DNR) inhibit the cooperative interaction of Akt and β-catenin at low doses [Fig.1]. These findings led to the repurposing of DXR as a targeted therapy to inhibit Akt:β-catenin interaction and specifically target chemoresistant LSCs in a mouse leukemia model. A pilot clinical trial (NCT02914977) applying these findings to relapsed/refractory adult leukemia patients has shown promising initial results [Fig.2]. [13

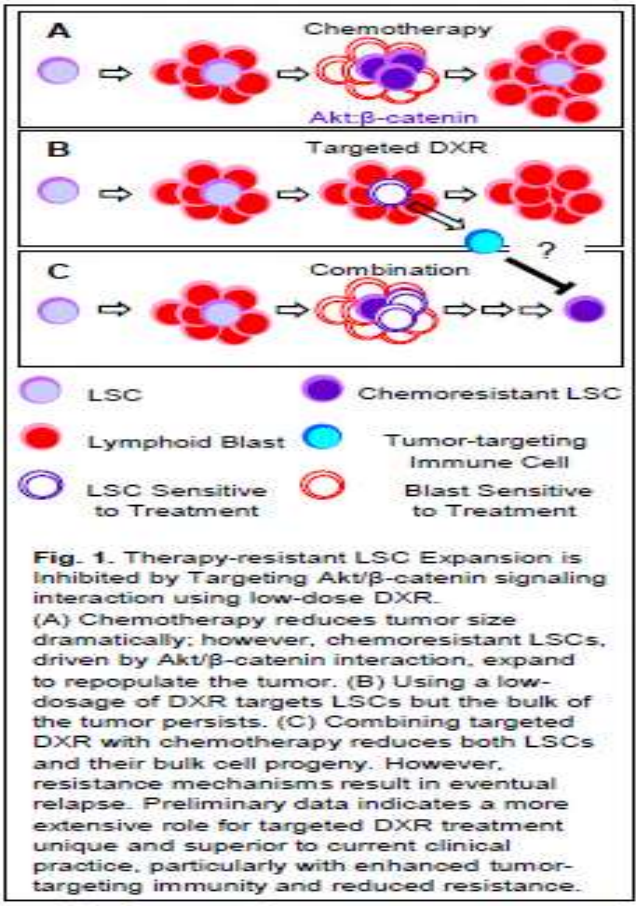

Fig. 1. Therapy-resistant LSC Expansion is inhibited by Targeting Akt/β-catenin signaling interaction using low-dose DXR.
(A) Chemotherapy reduces tumor size dramatically; however, chemoresistant LSCs, driven by Akt/β-catenin interaction, expand to repopulate the tumor. (B) Using a low-dosage of DXR targets LSCs but the bulk of the tumor persists. (C) Combining targeted DXR with chemotherapy reduces both LSCs and their bulk cell progeny. However, resistance mechanisms result in eventual relapse. Preliminary data indicates a more extensive role for targeted DXR treatment unique and superior to current clinical practice, particularly with enhanced tumor-targeting immunity and reduced resistance.

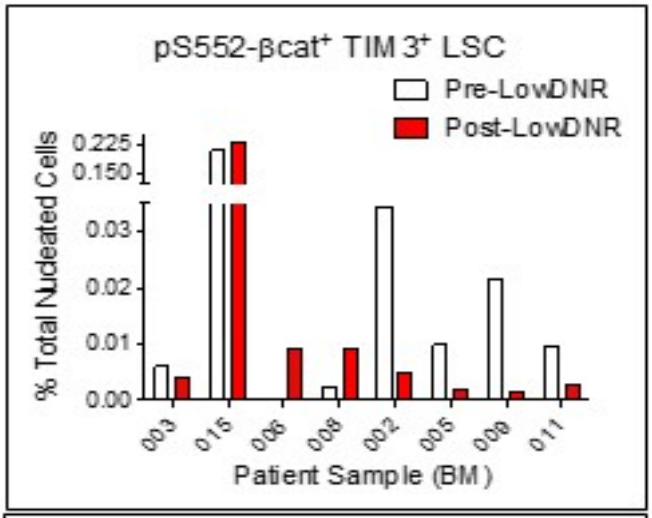

Fig 2. Low dose daunorubicin treatment was given to 8 patients with relapsed AML. 4/8 patients had reduction in LSC number after one cycle of therapy.

3.3 Optimal delivery of chemotherapeutic agents remains a key focus in preventing disease relapse. Current clinical practice using broadly toxic agents is generally immunosuppressive. Available preclinical data in murine models indicates that targeted DXR treatment expands cancer-targeting T-cells while inhibiting populations known to help cancer cells evade the immune system. Furthermore, targeted DXR treatment reduces immune checkpoint expression particularly on LSCs, potentially sensitizing LSCs to cytotoxic T-cells. These positive immunological "side" effects of targeted DXR treatment are negated or even reversed using the current clinical standard (high-dose) treatment in these models, which instead stimulates treatment-resistance mechanisms. However, since preclinical cancer research typically involves testing human cancer cells grown in culture or in immunodeficient mice, a significant knowledge gap exists in that therapy-induced anti-tumor immunity is largely unexamined but potentially critical for successful treatment.

Anthracyclines such as daunorubicin (DNR) and doxorubicin (DXR), have been the mainstays of childhood leukemia therapy both in upfront and relapse, for over 50 years. Targeted anthracycline therapy potentially reduces or eliminates minimal residual disease and chemoresistant LSCs in pediatric leukemia patients by inhibiting Akt:β-catenin interaction and/or reactivating anti-cancer immunosurveillance. This is currently being investigated in de novo children with leukemia, both AML and ALL (MARS study 13100340), and will be able to be compared to the baseline, days 8 and 29 results in this study.

4.0 Study Endpoints

If low dose daunorubicin is deemed feasible in this study, the next step would be to give traditional dose chemotherapy upfront in cycle 1, then await count recovery with minimal leukemia or minimal residual disease in end of induction bone marrow evaluation. This would be followed by low dose daunorubicin, waiting 14 days to repeat bone marrow evaluation to assess LSCs. Then move on with traditional cycle 2 chemo or a second low dose daunorubicin cycle. These would take place with a new protocol.

5.0 Study Intervention/Investigational Agent

DNR is an agent frequently used in the treatment of relapsed pediatric ALL and AML patients however it is not without long term side effects; primarily heart failure [8-10]. Cardiotoxicity is directly correlated with the cumulative dose of anthracyclines received. Cells responsible for leukemia relapse in children may be eliminated by repurposing DNR, at a significantly lower dose, as a targeted therapy to reactivate anti-cancer immunity while avoiding broad toxicity, particularly cardiotoxicity, and the evolution of resistance. The standard dose given in de novo AML is 50mg/m^2/day for 3 days and in de novo ALL is 25 mg/m2/dose once weekly for 4 weeks compared to the proposed dose of 6.75mg/m^2/dose for 5 consecutive days. We will also measure the pharmacokinetics of low dose DNR in these patients to enable preliminary PK-PD analyses and because there are essentially no PK data for DNR at comparable doses. Pharmacokinetics of low dose daunorubicin will be analyzed along with pharmacokinetics of standard doses of daunorubicin to assess for potential dose linearity relationship. Following participation on

this upfront window trial, patients who receive low dose daunorubicin can then proceed to other conventional or investigational therapies as clinically indicated

6.0 Procedures Involved

6.1 The proposed study is a prospective, upfront window, single-site investigation in study participants with relapsed/refractory ALL and AML. The study will be comprised of 10 pediatric patients receiving low dose daunorubicin, 1-21 years of age. At least 5 of these patients will not have undergone hematopoietic stem cell transplant (SCT). Once 5 SCT patients have been enrolled, subsequent SCT patients will be excluded and the study will remain open until a total of 5 patients without a history of SCT have been enrolled if not already accomplished. An additional 12 patients will be enrolled to receive standard dose daunorubicin for PK evaluation. Subjects will be identified through Hematology/Oncology at Children's Mercy Hospital. Subjects who meet all inclusion criteria and whose parents, after provided study information, provide written consent and patient assent if age appropriate, will be eligible for study Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

6.2 All subjects receiving low dose daunorubicin will begin Induction therapy with daunorubicin within 5 days of signing consent. In this pilot study, patients will be treated with 5 consecutive days of low dose daunorubicin, 6.75mg/m^2/dose given once daily IV over 10 minutes for one cycle. Dexrazoxane will not be co-administered owing to the very low dose daunorubicin used in this trial. Subsequent therapy after day 8 is at the discretion of the primary referring oncologist. During this study period, patients may be placed on hydroxyurea to aid in controlling hyperleukocytosis. Blood samples for evaluation of low dose daunorubicin pharmacokinetics (area under the time concentration curve, maximum concentration, elimination half-life, clearance) will be drawn prior to dosing and 5min, 20min, 40min, 1hr, 2hrs, 4hrs, 8hrs, and 24 hrs after dosing. LSC samples will be obtained at baseline, end of day 5 daunorubicin infusion, on day 8, day 29, with subsequent bone marrow exams, and upon count recovery from this or subsequent chemotherapy defined as an APC $\geq$ 500. A CBC with differential will be obtained on the same day as the initial bone marrow aspirate which is considered standard of care as well as daily during the chemotherapy administration. A CBC with differential will also be obtained on day 8 which is typically standard of care. These samples will be obtained on days when other labs are already obtained and thus no additional visits or central line entries are required.

PK analysis will also be performed in the additional 12 enrolled patients on standard dose daunorubicin with ALL and AML, 1-21 years of age, who are receiving daunorubicin as part of standard therapy. Blood samples for evaluation of standard doses of daunorubicin (0.67mg/kg/dose, 20mg/m2/dose, 25mg/m2/dose, 50mg/m2/dose) pharmacokinetics will be drawn at the same time points as those patients receiving low dose daunorubicin. Each blood draw for PK analysis will be 2-3ml unless patient weighs less than 8kg, in which case 1.5ml will be drawn to not exceed maximum allowed blood draw.

7.0 Data and Specimen Banking: NA

8.0 Genetic Analysis Information: N/A

9.0 Sharing of Results with Subjects

All disease and treatment related lab results will be shared with the subject, as per the standard practice within Hematology/Oncology, and any other CMH providers directly involved in the subject's care. PK results will only be shared upon subject request due to the lack of clinical significance to the subject.

10. Study Timelines

- Low dose DNR is designed in this study to be given for 5 days only. At any time, the patient may withdraw from study. The study therapy will be terminated if there are changes in the patient's condition which renders the patient unacceptable for further treatment in the judgement of the investigator. Patients who complete the 5 days of DNR, will be followed on study through collection of post-treatment disease assessments at count recovery not to exceed 60 days. The duration of an individual subject's participation in the study.
- Patients receiving standard doses of daunorubicin will be enrolled in the study for 24 hours
- Once IRB approval is received, study personnel will begin identifying and enrolling patients with an expectation that enrollment will be completed within 24 months. In parallel to recruitment, procurement and processing of patient samples as well as flow cytometry analysis of bone marrow and peripheral blood samples will occur. scRNA-seq genomic studies of the samples will begin in upon completion of patient enrollments. Data analysis will begin after the last enrolled patient has completed their treatment and 60 day follow-up period.
- Within 6-12 months, meeting abstract submissions, presentations, and publications (anticipated 2 to 3) will be developed from resultant data.

11 Inclusion and Exclusion Criteria

Inclusion Criteria for low dose daunorubicin

- Patients with pathologically confirmed ALL or AML, whose disease is refractory to two induction therapeutic attempts, or who are in 2nd or greater relapse, or who are in 1st relapse or refractory to a single therapeutic attempt but are unable to receive intensive therapy at the time of consent.
- All prior upfront therapies including bone marrow transplant are acceptable. Pulse steroids (of 5 days duration or less in the prior month) administered as part of a routine maintenance therapy are acceptable.
- Age 1 to 21 years of age, inclusive
- Established central catheter IV access

Additional Inclusion Criteria for PK analysis of standard dose daunorubicin

- Patients with pathologically confirmed ALL or AML, including patients with Down Syndrome, who will receive daunorubicin as part of routine chemotherapy decided by the primary oncologist
- Ages 1 to 21 years, inclusive

Exclusion Criteria

- Females who are known to be pregnant or lactating
- Any Grade 3 or higher Cardiac Disorder per CTCAE version 5
- Patients with echocardiographic evidence of cardiomyopathy (shortening fraction <27% or ejection fraction <50%)
- Uncontrolled sepsis
- Absolute Blast Count >50 x10(3)/mcL at enrollment or on day 1 of study
- Direct hyperbilirubinemia >5mg/dL
- Grade 3 or higher anaphylaxis to daunorubicin
- Non-English speaking
- Patients, who in the opinion of the PI, are unable to tolerate any study-specific procedures
- Patients who have received cyclosporine, tacrolimus or other agents to prevent or treat graft-vs-host disease post bone marrow transplant in the last 14 days
- Concurrent investigational drugs or other chemotherapeutic agents (excluding hydroxyurea), immunotherapies or biosimilars during the 5 days of daunorubicin.
- Prior cumulative doses of anthracyclines will not be an exclusion regardless of the total cumulative dose previously received.

Exclusion Criteria for PRK analysis of standard dose daunorubicin

- Patients who do not receive daunorubicin as part of their standard of care

The following populations will be excluded:

- *Adults unable to consent*
- *Prisoners*
- *Wards of the state*

12.0 Vulnerable Populations

12.1 Potential subjects will consist of mostly children. The primary physician/advanced practice nurse will initially approach potential patients. If a family and subject are interested in the study. The study will be further explained, and permission/assent/consent will be reviewed at this time, as will required

assessments for the study. Ample time and opportunity are provided to the child and family to ask about the details of the study, to consider other available options, and to decide whether to participate. We will be obtaining permission from at least one parent for study participation of minors. Assent will be obtained from all children at least 7 years of age and will be documented in the Child Permission/Assent form. Authorized personnel will document assent in the Child Permission/Assent form. The study will be directly explained to the minor in simpler terms that he/she will understand. The family will be given copies of the consent or permission/assent as well as contact information for the site PI.

13.0 Local Number of Subjects

The total number of subjects to be accrued to receive low dose daunorubicin: 10 who will have completed the prescribed 5 days of therapy.

The total number of additional subjects accrued for PK analysis: 12

14.0 Screening and Recruitment Methods

14.1 Potential subjects will be recruited once determined they meet inclusion criteria. This may take place in Children's Mercy Hospital Participants will be approached to provide informed consent or assent to enter the proposed study.

14.2 Subjects will be patients of Children's Mercy Hospital.

14.3 Potential subjects will be identified by provider referral.

15.0 Withdrawal of Subjects

15.1 Patients can be taken off the study treatment at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient is unable to comply with protocol requirements;
- Patient experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician judges continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

15.2 Patients who are removed from the study prior to the completion of 5 days DNR due to disease progression or adverse events attributed to daunorubicin will continue to have their data reported from the time prior to study withdrawal. Patients removed from the study for any

other of the above reasons in addition to voluntarily withdrawing, will not have data reported.

16.0 Risks to Subjects

16.1 All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects. Side effects are usually reversible when the medication is stopped but occasionally persist and cause serious complications. A person can die from these and other complications. People who do not undergo treatment will have side effects due to their disease.

Common side effects of Daunorubicin include nausea, vomiting, hair loss, fatigue, red colored urine for 2 days after treatment, and loss of appetite. Drugs may be given to prevent or decrease nausea and vomiting. Hair loss is usually temporary but on very rare occasions, it may be permanent. Some chemotherapy may lead to sterility. There is also a possibility that a second cancer may develop years later as a result of chemotherapy.

Daunorubicin is not an IND agent. It is FDA-approved and used in this protocol within an approved indication. This study does not involve any factors that would significantly increase the risk associated with daunorubicin.

16.2 The risk involved in this study is Category 2 as highlighted below.

16.3 No procedures will have risks that are currently unforeseeable.

16.4 As the effect of Daunorubicin on an embryo or fetus is not fully understood, it will not be administered to any pregnant persons.

16.5 There are no risks to those who are not subjects.

17.0 Potential Benefits to Subjects

Daunorubicin is an agent frequently used in the treatment of relapsed pediatric ALL and AML. Daunorubicin is a cytotoxic anthracycline chemotherapy isolated from the culture of *Streptomyces.* It acts through inhibition of topoisomerase II and DNA intercalation leading to cell death. It is commonly used at high doses in the treatment of both AML and ALL.

18.0 Investigator Assessment of Risk/Benefits Ratio: **(IRB makes the final determination)**

Select as applicable:	**Pediatric Risk Category:**

	Category 1	Research not involving greater than minimal risk (45 CFR §46.404 and 21 CFR §50.51)
X	Category 2	Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. (45 CFR §46.405 and 21 CFR §50.52)
	Category 3	Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. (45 CFR §46.406 and 21 CFR §50.53)
	Category 4	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (45 CFR §46.407 and 21 CFR §50.54)
Select if applicable:	**Adult Risk Category:**	
	Not Greater than Minimal Risk	
x	Greater than Minimal Risk	

19.0 Data Management and Confidentiality

19.1 The sample size for this study was determined based on number of relapsed leukemia patients in recent years as well as in coordination with a Children's Mercy statistician.

19.2 Each patient will be assigned a study number. No other subject identifiers will be used on data forms. Subject data will be stored in a confidential database that does not contain patient protected information or identifiers. A separate list linking the study numbers to the patients will be maintained electronically in a password-protected sector of the CMH server. Only CMH research personnel will have access to this data. All personal information (e.g., PHI) will be kept confidential.

19.3 Certificate of Confidentiality – NA

19.4 Stored samples will be labeled with the IRB protocol number and the patient's assigned study number only. This will be clearly stated in the consent form. If a participant withdraws prior to completing the study; the specimens and the data collected from that individual will not be included in the final data analysis. All data will be stored with numerical identification and files will be kept in locked offices and or password-protected encrypted electronic files. Personal identity will be protected in any publication. Whether associated with the storage/retention of protected health information or the dissemination of study results, the CMH policies pertaining to HIPPA and the storage of research data will be followed.

19.5 Records to be kept/Secure Storage of Data

Each subject will be assigned a study number which will be used for data collection. No other subject identifiers will be used on data collection instruments. Per hospital policy, the subject's permission/assent/consent document will be labeled with the subject's name and medical record. The original will be

maintained in the study chart and an electronic version will be scanned into the subject's medical record. Data will be stored in a password protected database. Access will be limited to study personnel. A separate list linking the study numbers to the patients will be maintained electronically in a password-protected sector of the CMH server. Only CMH research personnel will have access to this data. Samples will be labeled with the IRB protocol number and the patient's assigned study number only. This will be clearly stated in the consent form.

20.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Feasibility will be determined based on multiple observations. Feasibility failure due to progressive leukemia is defined as a rise in ABC of >10,000/day on two consecutive days that continues to increase >10,000/day after starting hydroxyurea. Low dose daunorubicin will also be deemed not feasible if there is evidence of progression of extramedullary leukemia, or if the patient experiences uncontrollable nausea and/or vomiting. Low dose daunorubicin will be reported as not feasible as upfront treatment if more than 3 patients are unable to complete all 5 doses of the drug. If the patient is hospitalized for any reason except the aforementioned, low dose daunorubicin will still be considered feasible. Complications leading to interruption in ability to dose daunorubicin consecutively such as need for surgery not attributable to daunorubicin will not be a marker of feasibility.

The DSMB of the University of Kansas Cancer Center will be responsible for monitoring patient safety for this trial. Their monitoring will include review for progress and safety, review of adverse events, and review of any other component of the study identified by the DSMB.

21.0 Provisions to Protect the Privacy Interests of Subjects

21.1 Confidentiality of all subjects participating in the trial and all of their medical information will be maintained. All CRFs and any identifying information will be kept in a secure location with access limited to the study staff directly participating in the trial.

21.2 Subjects will be provided with study contact information for any questions or concerns that arise before, during and after the study.

21.3 While confidentiality cannot be guaranteed, PHI will be protected to the greatest extent possible. There also may be some situations where laws require the release of PHI. If PHI is shared with an organization that is not required to comply with federal privacy laws, health information is no longer considered protected and may be used and shared freely by that organization.

21.4 PHI to be accessed and/or recorded for this research study: name/initials, date of birth, date of death, dates of service, medical record number, telephone number, and hospital account number.

21.5 The research team will not be obtaining a HIPAA Waiver for this study.

22.0 Compensation for Research-Related Injury

22.1 In the case of illness or injury resulting from this study, treatment is available at Children's Mercy Hospital, but will be provided at the usual charge. Payment for this treatment will not be provided by the sponsor of this research study. The hospital may not be able to bill insurance or other third party payers for this care. The Children's Mercy Hospital does not have funds set aside to pay research participants if the research results in injury. Children's Mercy Financial Counselors may be able to help families find funds to help cover the cost of medical services. If a subject experiences difficulty paying for services not covered by insurance, a Financial Counselor can be reached at 816-234-3567.

23.0 Economic Burden to Subjects: NA - All research related activities are funded by the study.

24.0 Permission/Assent/Consent Process

Consent will be obtained in person within the HEM/ONC division. Permission/assent/consent will be obtained upon initial discussion with the patient. We will be following CM research policies on informed permission/assent/consent. If we need to obtain permission/assent/consent via telephone, we will be following CM research policy.

Subjects who are not yet adults (infants, children, teenagers)

- All children 7 years and older will be assented.
- Child assent will be documented in the medical record. If a child is unable to assent, this too will be documented in the medical record
- Consent at 18 years of age, when minor subjects become adults. The child will be reconsented at the age of 18 if previously assented as a minor.

25.0 Process to Document Permission/Assent/Consent

25.1 We will follow CM Research Policy 10.04 Obtaining Permission/Assent/Consent process.

26.0 Setting

26.1 The research team will conduct research within the heme/onc division.

26.2 Pharmacokinetic analysis will be performed at University of Kansas Medical Center PACKAGING AND TRANSPORT OF SPECIMENS

- Research Staff will complete a label which will have the assigned study number along with date and time of draw and location on study tubes. The results will be analyzed by the PI of this protocol.
- If study is obtained prior to 1:00, study tubes will be placed in marked transport container along with ice pack, wrapped in toweling, and taken to the Main Lab at CMH.
    - Research staff will notify CMH lab staff of delivery.
        - Staff will confirm delivery to University of Kansas Cancer Center between 3:30-4pm the same day.
        - CMH courier will transport samples to University of Kansas Cancer Center **security desk in the research building**
        - University of Kansas Cancer Center security will alert cytometry staff to pick up samples
        - CMH Security will pick up new container and return it to the main lab at CMH.
        - Research Staff will pick up the container as soon as possible.
- If study is obtained after 1:00pm, study tubes will be refrigerated overnight. Tubes will be packed and taken to the lab prior to 1:00 the next day.

27.0 Resources Available

- The goal accrual for this study is 22 subjects which will be feasible in the allotted time frame.
- As this research project is vital to fellowship graduation, a lot of time will be devoted to this research.
- Children's Mercy Hospital is a free-standing children's hospital with a hematology/oncology division that participates in many research projects.
- Research subjects have access to medical as well as psychological care within the heme/onc department.
- All persons assisting with the research are met with periodically to stay abreast of the protocol, procedures, etc.
- Dr. Alan Gamis and Dr. Susan Abdel-Rahman are providing mentorship.

28.0 Multi-Site Research: NA

29.0 International Research – N/A