Trial Protocol
NCT#02708108

Initial Protocol Date: April 4, 2016

Amendment #1: May 31, 2016
Amendment #2: June 29, 2017
Amendment #3: October 18, 2017
Amendment #4: May 3, 2018

Improving **D**iet and **E**xercise in **A**cute **L**ymphoblastic Leukemia (IDEAL Weight in ALL Trial): Environment and Microenvironment #3

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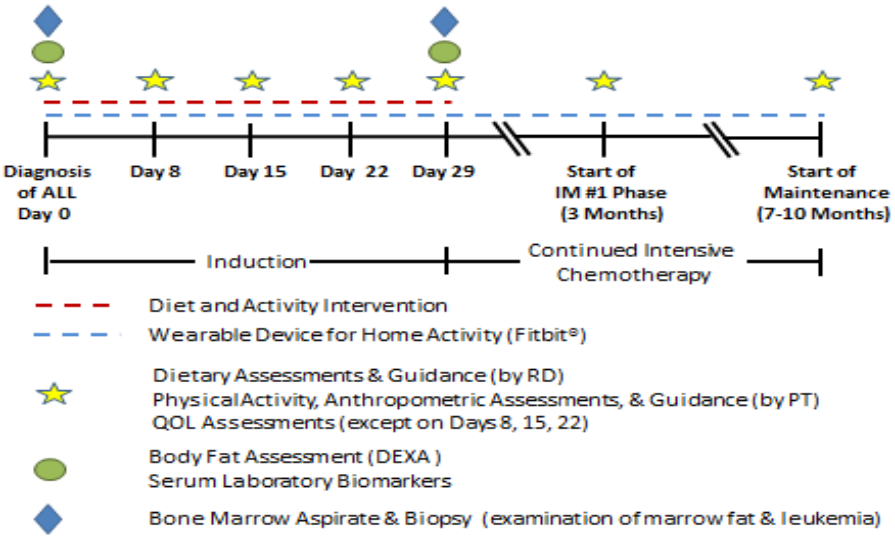
ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy with almost 2,000 children diagnosed per year in the United States alone. While 5-year event-free survival rates have topped over 90% in the past decade, overweight and obese pediatric ALL patients have a 50% greater risk of relapse than normal weight children. With about 1 in 6 US children being overweight or obese, it is urgently necessary to combat the negative role of obesity on ALL treatment in the clinical setting.

In our previous study, we have observed that: 1) nearly half ALL patients are overweight or obese at diagnosis, 2) all patients, regardless of starting weight, gain significant fat mass over the first month of therapy (on average 20-30%), and 3) obesity at the time of diagnosis is associated with a higher likelihood of poor response to chemotherapy as evidenced by persistent leukemia (minimal residual disease) after induction therapy. Together, these data show that body fat is a significant risk factor for ALL treatment failure, and that its negative effects are evident within the first month of treatment. Recent laboratory and clinical data illustrates the ability of diet restriction and physical activity to improve chemotherapy efficacy, reduce treatment-related toxicities and better overall quality of life.

However, to our knowledge, no clinical trial has demonstrated the efficacy of such a comprehensive, integrative medicine approach to improve chemotherapy efficacy and quality of life in ALL patients during intensive therapy, let alone any pediatric cancer population. Given the importance of successful induction therapy in predicting long term survival and the negative role of obesity on treatment success, we are proposing a complete personalized dietary and exercise intervention for pediatric ALL patients that aims to reduce fat gained during induction therapy, thereby improving their treatment response and also quality of life.

EXPERIMENTAL DESIGN SCHEMA



1.0 GOALS AND OBJECTIVES

1.1 Hypothesis:

In pre-adolescents, adolescents, and young adults (AYA) diagnosed with NCI/Rome High-Risk B-precursor acute lymphoblastic leukemia (HR-ALL), reducing gains in adiposity (i.e. fat mass) will improve leukemia sensitivity to induction chemotherapy, reduce post-induction minimal residual disease (MRD), reduce fatigue and obesity-associated toxicities, and improve quality of life.

1.2 Primary aim:

In AYA patients newly diagnosed with HR-ALL, to quantify the impact of a personalized dietary and activity intervention to mitigate chemotherapy-induced body fat gain throughout the critical first month of treatment ("induction").

1.3 Secondary aims:

In AYA subjects newly diagnosed with HR-ALL:

1. To compare the rate of leukemia “positive” minimal residual disease (MRD) in the bone marrow at end of induction (≥0.01% mononuclear cells) in those who received the intervention as compared to a historical controls.

2. To assess adherence to, and feasibility of, implementing a personalized and comprehensive dietary and exercise intervention during the first month of intensive chemotherapy

1.4. Exploratory aims:

In AYA subjects newly diagnosed with HR-ALL:

1. To evaluate persistence or extinguishing of this effect over months of continued dose-intensive pre-Maintenance phases of chemotherapy
2. To characterize the direct impact as compared to baseline of the intervention on self- and family- reported quality of life (QOL) outcomes including fatigue, mood, social interaction, and cognitive impairment reported via the PedsQL questionnaire and Child and Adolescent Scale of Participation (CASP) following the induction phase and serially during dose-intensive phases of chemotherapy.
3. To quantify the effect of adiposity on the activity of leukemogenic JAK2/STAT3, PIK3K/AKT/mTOR, MAPK/ERK , and other signaling pathways in leukemia cells as determined by kinase phosphorylation.
4. To quantify the effect of adiposity and of the intervention on the metabolic activity of leukemia blasts and of adipocytes as assessed by IGF-1, other obesity-associated cytokine signaling pathways, adiponectin, leptin, free fatty acid synthesis and metabolism, and levels oxidative stress.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 INTRODUCTION

Obesity is a major cause of morbidity and mortality in the U.S. and worldwide. We and others have shown that obesity increases the risk of cancers such as leukemia, and can impair leukemia treatment and patient survival (1-3). In adults treated for breast and colorectal cancer, altering nutritional intake and increasing physical activity during treatment improves efficacy (4,5) while limiting treatment symptoms like fat gain and fatigue (6). In this proposed study, we will explore how a dieting and exercise intervention throughout the first month of treatment may counteract the adverse impact of body fat on leukemia therapy efficacy, toxicity, and quality of life.

2.2 FAT MASS AND ALL

Obesity increases the incidence of many cancer types, and obese cancer patients have a higher risk of mortality from their disease (3). In 2007, a landmark study in the Children's Oncology Group (COG) led by Dr. Butturini from the Children's Hospital Los Angeles (CHLA) demonstrated in two large cohorts (4,314 and 1,160 patients) that obesity at the time of diagnosis increases risk of relapse in children with National Cancer Institute/Rome High-Risk B-precursor ALL (HR-ALL) by 50% (1), a finding independently confirmed in a different population of children (7) in obese adults (8), and by meta-analysis (2). In a recent study, 36% of children with ALL were overweight or obese at diagnosis (9), while in another cohort 23% of children with HR-ALL continued to be obese throughout therapy (10). In our earlier cohort of adolescent and young adults with HR-ALL treated at CHLA, we found an even higher prevalence of high body fat whereas 48% were overweight or obese at diagnosis. Our data also showed that all individuals – both those lean and those obese- gain a significant amount of adipose tissue during the first month of treatment alone ("induction"). On average, patients gained ~20-30% of fat above their starting body fat percentage. The use of glucocorticoids such as dexamethasone and prednisone during induction therapy likely contribute to this fat gain, as they stimulate adipogenesis and appetite. Predisposition to inactivity due to intensive leukemia treatment combined with steroid-induced dietary derangements are therefore likely moderating factors of this marked gain in body fat. As response to leukemia treatment in the first month of therapy is a key determinant of overall prognosis and risk for relapse, and as obesity and body fat are risks factors for relapse, an intervention aimed at reducing the gain in body fat has potential to improve leukemia therapy efficacy starting from the initial time of diagnosis.

2.3 DIETING, ACTIVITY AND CANCER

The concept of introducing caloric restriction in animal cancer models has been explored throughout the last century (11). Recent experiments have focused on the theory of "differential stress resistance," a diet restrictive metabolic state that increases normal tissue, but not cancer cell, tolerance to chemotherapy (12). During carcinogenesis, cancer cells acquire mutations to various metabolic oncogenes, such as Akt and Ras, which allow uncontrolled proliferation. During dietary restriction and the subsequent lack of nutrients and growth factors, normal cells down-regulate their metabolic activity while cancer cells

maintain their elevated metabolic state, a condition that promotes greater chemotherapy specificity toward cancer cells. This was demonstrated in a transgenic mice with human neuroblastoma fasted for 48 hours prior to etoposide treatment. The fasted mice not only survived longer than non-fasted mice but also suffered less drug-induced toxicity (13).

While such a severe starvation diet is not feasible in the clinical setting, altering dietary composition and/or reducing caloric intake is sufficient to see similar results. In a murine prostate cancer model, mice fed with either a low-fat or no-carbohydrate diet had significantly reduced tumor growth compared to mice on a "Western" diet (14). Similarly, a low carbohydrate, high protein, isocaloric diet limited squamous cell carcinoma and breast cancer growth in mice (14).Even restricting total caloric intake during treatment by 30% regardless of dietary makeup reduced breast tumor aggressiveness and tumoral fat content (15). Our own preliminary research (described below) has demonstrated a similar effect of caloric and fat restriction on reducing weight and improving survival of obese mice with ALL.

Physical activity during therapy has also been shown efficacious to augment cancer sensitivity. Mice that were allowed to run on a wheel had slower breast tumor growth and improved immune function compared to non-exercised mice (16). Furthermore, the amount of running inversely correlated with the size of the tumor. Similarly, serum from men who exercise for one hour prevented prostate cancer growth *in vitro* compared to cells in serum from non-exercising men (17). Despite this history and the breadth of research into diet and exercise interventions as adjuvants to chemotherapy, the translation of these laboratory findings into the clinical setting has remained a barrier.

Diet and exercise have concrete benefits in addition to potentially augmenting chemotherapy efficacy. Multiple clinical trials conducted in the last ten years have demonstrated the ability of diet and/or exercise to prevent chemotherapy-associated fat gain, reduce fatigue and improve emotional well-being in adults with solid tissue and hematological cancers (5, 18, 19). Furthermore, the American Cancer Society has recommended that proper nutrition and physical activity play a role in all phases of cancer treatment (20).

2.4 DIET AND ACTIVITY INTERVENTIONS FOR OBESITY

With 16.9% of 2-19 year olds being obese (21) and at risk for serious co-morbidities (22), there is a necessity for effective obesity-targeted pediatric interventions. While many interventions have long existed for obese adults, their efficacy in obese children has only begun to be explored recently. Obese children without cancer randomized to an intervention prescribing 90 minutes of moderate exercise three times per week, a hypocaloric diet, and weekly meetings with a dietician had a lower BMI, body fat percentage and LDL cholesterol level than children receiving only individual diet or exercise (23). Similarly, a 16 week low-carbohydrate plus aerobic and strength training intervention proved more effective in reducing BMI, body fat and fasting glucose compared to diet or exercise alone (24).

2.5 QUALITY OF LIFE DURING ALL THERAPY

As the treatment for ALL has become more successful, the assessment and improvement of patient QOL are becoming the focus for new studies and treatment modalities. To date, multiple assessment tools

have been developed to assess QOL in the pediatric cancer population. One such tool, the Pediatric Quality of Life Inventory (PedsQL), in conjunction with the PedsQL 3.0 Fatigue Module, has been shown to be particularly effective in assessing physical, emotional and social functioning, fatigue, pain, nausea, anxiety and cognitive problems among others (25).

Using this assessment tool, it has been shown that children actively undergoing chemotherapy have a lower QOL than healthy children (26) or even those 1 year removed from chemotherapy (27). Additionally, researchers have measured the changes in patient QOL over the course of ALL therapy. In patients with SR-ALL or HR-ALL, nausea, procedural and treatment anxiety and worry were worse during induction compared to maintenance therapy (28). Another similar study demonstrated a lower health-related QOL in patients in induction therapy compared to all other phases of treatment (29).

Little research has been performed to analyze the effect of physical activity on QOL in ALL patients undergoing chemotherapy. One randomized trial demonstrated improved QOL in pediatric cancer patients, including those with ALL, who participated in physical activity sessions during hospitalization (30). In adolescent survivors of ALL, leisure-time physical activity was also associated with improved QOL (31). Greater research is needed to better understand the ability of physical activity, and dietary intervention, to improve patient QOL during and after chemotherapy.

2.6 STUDY SIGNIFICANCE

To our best knowledge, no clinical study has reported the effect of a combined diet and activity program as an adjuvant to chemotherapy in overweight and obese pediatric patients with any cancer diagnosis. However, with the combined expertise of our integrative medicine team of dieticians, physical therapists, oncologists and endocrinologists, we are confident that a comprehensive obesity-targeted intervention will reduce fat gain and lean muscle loss to improve treatment efficacy and QOL during therapy. The intervention will have the added benefit of promoting healthier lifestyle choices throughout the rest of treatment and into adulthood.

3.0 PRELIMINARY DATA

Obesity is a common problem in our patients with ALL.
In our cohort of adolescents with HR-ALL at CHLA, 48% were overweight or obese at diagnosis. Further, from the time of diagnosis to the end of the induction phase, subjects had an ~25% increase in body fat over these first 28 days of chemotherapy alone (from 23.3±9.1% at time of diagnosis to 33.7±9.8% at end of induction, p<0.001, Fig. 1). Even more striking, this gain in body fat pecentage was present in the entire cohort regardless of starting body composition (Fig 1.). Body fat then increased even further, to a mean of 37.1±7.9% by the end of Delayed Intensification, following approximately seven months of intensive chemotherapy (p<0.001, not shown). Overall, this increase in body fat represents a gain of 5.2±4.9 kg of adipose tissue over the entire study period. Given our findings that adipose tissue can directly impair chemotherapy efficacy on ALL (32,33), this gain in body fat during such the critical chemotherapy dose-intensive treatmentr period is very concerning.

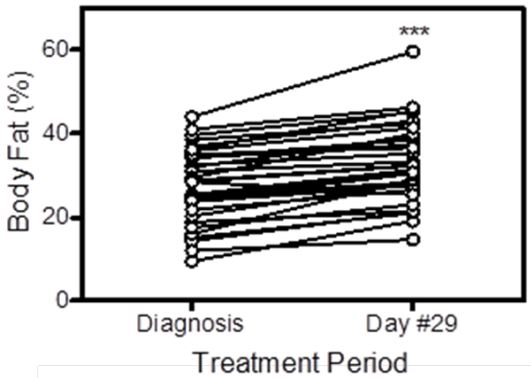


Fig 1. Body fat percentage measured by DXA scan in 10-21 year old children at diagnosis and end of induction. ***p<0·001

Obesity impacts ALL survival within the first month of treatment. Treatment for childhood ALL generally lasts for 2-3 years. The first month of treatment (induction) is intense including prolonged high doses of steroids, and weekly chemotherapy, and frequent physician visits. Response to induction therapy through clearance of leukemia from the bone marrow as measured by flow cytometry and reported as "minimal residual disease" (MRD) is generally accepted as one of the best predictors of long-term survival (34). Given the association observed between obesity at diagnosis and EFS (1), we examined whether weight status at diagnosis would increase the risk of residual leukemia at the end of induction as measured by MRD. To do this, we retrospectively evaluated the records of 198 children treated at CHLA for B-precursor ALL. We observed that MRD positivity (as defined per COG by MRD with multicolor flow cytometry ≥0.01%) was increased in children who were overweight or obese (Fig 2 above).

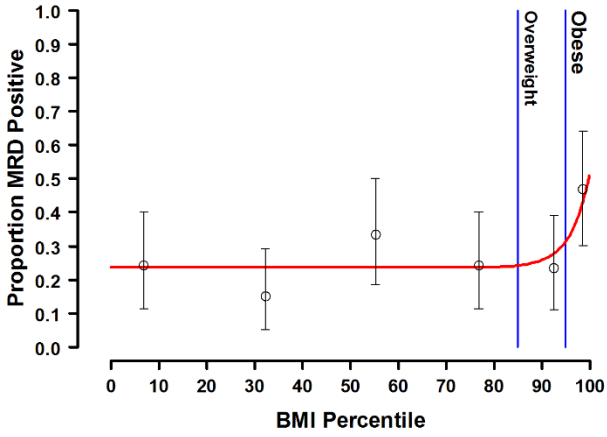


Fig 2. BMI percentile and MRD positivity (≥0·01%).

The strongest association was in obese patients, who had a statistically and clinically significant higher risk of persistent MRD (Odds ratio 2.5, 95% CI 1.2 – 5.1, p = 0.014, adjusted for NCI risk group and validated leukemia risk factors) but with increased risk present in the overweight too (OR 1.37, p=0.046 for the three weight-group analysis). Evaluation of BMI percentile as a continuous variable further confirmed increased prevalence beginning in the overweight range (Fig. 2). Thus, the effect of overweight and obesity to worsen EFS is present during Induction.

The effects of obesity are reversible. As weight is not static during ALL therapy (10), we recently evaluated the effect of duration of exposure to extreme weight on survival (Fig. 3, 35). In a restrospective COG study led by Orgel et. al., in 2,008 children with HR-ALL, we determined that while children who were obese for greater than 50% of the early intensive chemotherapy phase had a poorer event free survival (HR of event = 1.43 [1.04-1.96] compared to those of "normal" weight), obese children whose weight normalized out of the obese range for more than 50% of the time of early intensive therapy had an improved outcome similar to those never obese (HR = 0.99 [0.62-1.58]). <u>These data suggest the effect of obesity might be reversible.</u>

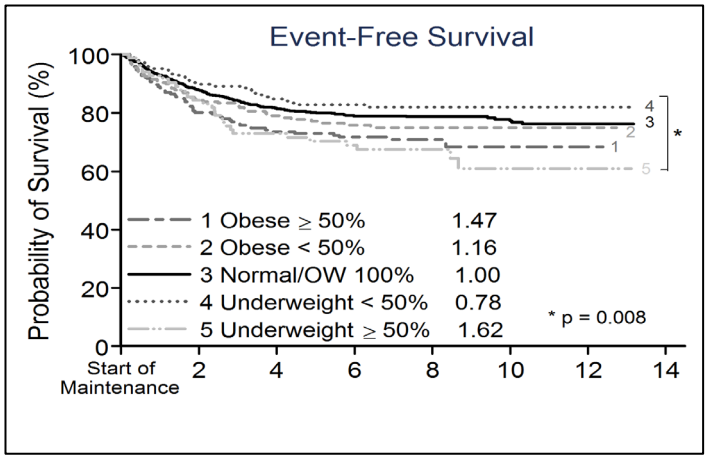


Fig 3. EFS per BMI during HR-ALL Therapy

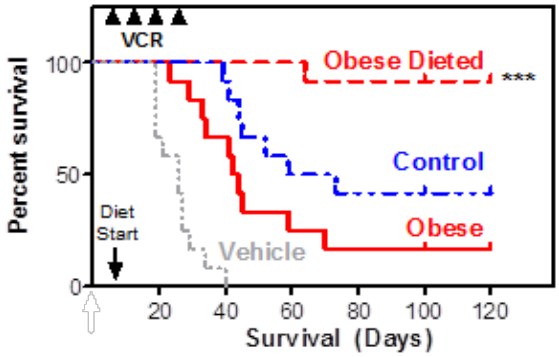


Fig 4. Diet affects ALL survival. Dieted mice were switched to 10% fat diet on day 7, when vincristine (VCR) treatment was initiated.

To address this important question, we designed experiments to determine whether or not dietary intervention that was initiated when leukemia is diagnosed could improve outcome. Diet-induced obese (DIO) mice and matched controls were transplanted with ALL cells and chemotherapy with vincristine (VCR) was initiated 7 days after transplant, as previously described (32). At this point, half of the obese mice were switched to a low (10%) fat diet. Thus, this experiment simulated the clinical condition in which a dietary intervention could be initiated at the time of diagnosis, namely at the same time that chemotherapy would be started. Remarkably, obese mice switched to a low fat diet had a substantially improved survival compared to the non-switched animals ($p<0.001$), and even survived longer than controls that had been raised on the low fat diet ($p<0.01$, Fig 4). <u>Thus, switching mice from high fat to low fat diet when treatment is started substantially improves leukemia survival.</u>

Obesity increases toxicity. As part of the same COG desribed above (Orgel et. al)., we also evaluated obesity as an ongoing risk for toxicity. In doing so, we found a striking effect of obesity on toxicity within each phase of pediatric ALL chemotherapy for children with HR-ALL: in 2,008 children (representing 13,946 cycles of chemotherapy), obesity was associated with increases in hepatic (OR = 1.32 [1.15-1.51], $p<0.001$) and pancreatic (OR = 1.53 [1.22-1.92], $p<0.001$) toxicity within each cycle of chemotherapy as compared to lean or underweight children. Toxicity affecting the liver and pancreas are specifically

notable in ALL regimens as they limit our ability to deliver optimal dosing of chemotherapy. Of note, and germane to the secondary objectives of this proposal, obese children also suffered from reduced strength during therapy (OR = 1.33 [1.08-1.64], p<0.001) as compared to those lean/underweight. Healthy reduction in body fat therefore has significant potential to not only improve survival, but to reduce key toxicities during ALL therapy.

Physical activity can be targeted in ALL. In a recent pilot study on preferences for physical activities and engagement in children and adolescents with ALL, we assessed 37 patients ages 10-18 (68% male; 65% Latino) using the Activity Preferences and Participation Scale (APPS), a newly developed measure designed to identify activity preferences, activity frequency, and social engagement in activity. The tool was administered on an iPad, and included perceptions of activity levels, self-reported changes in activity levels since diagnosis, and perceived barriers to engaging in physical activity and the importance of physical activity. Of the participants, 14 were in the induction/consolidation phase of treatment, 12 in Maintenance, and 11 off- treatment. Forty percent of individuals in the sample were overweight or obese. At all phases of treatment, participants strongly preferred and participated in sedentary activities. There was a high correlation between activity preference and activity participation in moderate-vigorous activities. Of particular relevance to the present study is that more than half of the participants in the induction/consolidation phase stated that fatigue, poor balance or weakness, and energy levels were barriers to participation in physical activity, while approximately 1/3rd reported that feeling sick or nauseated was a barrier. Most participants reported being less physically active since they were diagnosed with ALL, with the greatest declines reported in the induction/onsolidation (100%). All participants reported that they would like to be more physically active. As would be anticipated, induction chemotherapy fosters a non-active lifestyle; an integrative medicine intervention educating subjects and families how to safely exercise is both urgently needed and desired by families.

4.0 SCREENING AND ENROLLMENT

4.1 SUBJECT IDENTIFICATION

Physicians who wish to enroll patients should first contact the local site's research coordinator to determine if the study is currently open to accrual. Patients with newly diagnosed HR-ALL greater than or equal to 10 years of age are to be identified for eligibility screening by the oncology care team and/or study investigators. Screening logs with a coded identifier are to be maintained by each site; for eligible subjects not enrolled, the reason should be recorded.

4.2 IRB APPROVAL

Local IRB approval at each site must be confirmed by the research coordinator prior to enrolling a patient.

4.3 SCREENING PROCEDURES

Studies or procedures performed solely for clinical indications (and not done for purposes of determining study eligibility) may be used to screen for initial study eligibility and thereafter may be used for baseline values even if the studies were done before informed consent was obtained.

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent.

4.4 INFORMED CONSENT/ASSENT

Potential subjects and/or their parent(s) or guardian(s) (as applicable) will have the following carefully explained as described in the IRB-approved consent/assent documents: (1) the investigational nature of the research, (2) the objectives of the research, (3) the procedures involved in the research, and (4) any and all risks and discomforts due to participation. Clarification questions will then be elicited from the potential subject and/or their parent(s) or guardian(s). Only afterwards will an informed consent and assent document be signed as per institutional guidelines, with a copy to be given to the patient and the original placed in the research record.

Study participants are to be consented by the study investigators during their routine comprehensive study consent conference and/or by study investigators. As is the departmental standard practice regarding opening and accruing patients to clinical trials, care teams are to be fully briefed about the study details prior to study opening and will have the opportunity to ask clarifying questions. In addition, care teams will be kept apprised of any developments in study operation over the course of the study. Study investigators will also be available at all times to clarify any questions prior to the consent conferences.

4.5 CONTACT REQUIREMENTS

After eligibility requirements are met as per below, the principal investigator should be notified via email of subject eligibility and enrollment status.

4.6 ELIGIBILITY CHECKLISTS

The "Eligibility Checklist" must be completed, signed, and dated by the clinical research coordinator (or study investigator) prior to official study enrollment. This form must then be maintained in the study record.

4.7 STUDY ENROLLMENT

Once all applicable eligibility requirements are met, the patient will be enrolled in the study by the research coordinator.

Timing of Enrollment: Patients will ideally be enrolled prior to starting systemic chemotherapy (not including steroid pre-treatment/steroid prophase) but must be enrolled within 24 hours of starting systemic chemotherapy. Enrollment after 24 hours of starting systemic chemotherapy will be allowed at the discretion of the PI (or delegate) though the end of "chemotherapy day" 4.

4.8 PATIENT REGISTRATION

After subjects have been enrolled on the study, the **coordinating center (CHLA) will assign a unique study identifier to be emailed to each site.** Thereafter, they will be identified only by this unique identifier. All medical information will be protected as per the section below on "Records and Reporting."

5.0 PATIENT CRITERIA FOR ELIGIBILITY

The eligibility criteria listed below are to be interpreted literally. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical and research record which will serve as the source document for verification at the time of audit.

5.1 INCLUSION CRITERIA

Subjects:

- Are greater than or equal to 10 years of age and less than or equal to 21 years of age at time of diagnosis
- Have a new diagnosis of untreated NCI/Rome High Risk B-precursor ALL (HR-ALL)
- (with the exception of steroid pre-treatment/steroid prophase or the administration of intrathecal chemotherapy)
- Are beginning treatment on- or as per- a CCG-COG[1] protocol with a 4-drug Induction including vincristine, daunorubicin (or doxorubicin), asparaginase, and at least 14 days of glucocorticoid steroids

5.2 EXCLUSION CRITERIA

Subjects cannot:

- Have a diagnosis of Down syndrome (Trisomy 21) or any genetic disease associated with abnormal body composition
- Be underweight or "at risk for underweight" with moderate weight loss, defined as a starting Body Mass Index (BMI) <10th percentile for age and sex (for those >20 years of age, defined as an absolute BMI < 18.5)[2]
- Have pre-existing abnormal intestinal function (e.g. protein-wasting enteropathy, fat malabsorption)
- Be unable to comply with both the recommended diet and activity interventions (as determined by study or treatment team)
- Have a history of prior chemotherapy or radiation for other cancers
- Be unable to complete the necessary radiology examinations with fully interpretable data (e.g. hip replacement and metal prostheses preclude evaluation by DXA)
- Be pregnant (to be confirmed by urine or serum pregnancy test as per institutional routine care for chemotherapy and radiology exams)

[1] COG = Children's Oncology Group. CCG = Children's Cancer Group

[2] Per the latest definition of Center for Disease Control and Prevention, underweight is defined for those <20 years of age as a BMI <5th percentile for age and sex and an absolute BMI <18·5 in adults >20 years of age. "At-risk for underweight" is a study-specific definition outlined above.

5.3 CONCOMITANT THERAPY

Patients may be receiving concurrent therapies including investigational agents for the treatment of their underlying malignancy.

5.4 CO-ENROLLMENT ON RESEARCH STUDIES

As per the Children's Oncology Group (COG) standard practice, this study is a behavioral intervention and does not include an investigational agent and is therefore not excluded from co-enrollment on COG trials. Moreover, the study behavioral intervention occurs during a treatment period (induction) where no COG or other research intervention is planned through the duration of this protocol. Of note, the relevant COG trial AALL1131 specifically outlines multiple concomitant therapies that are excluded but does not include behavioral interventions such as this one. For patient specimens, collection of samples for research will be coordinated closely with the clinical leukemia team; should a conflict arise for patient samples, priority will be first accorded to clinical care. Second priority will then be afforded to COG studies required for co-enrollment on COG therapeutic trials. Following both these uses, remaining sample will be obtained for this research study.

6.0 STUDY PLAN

6.1 SUMMARY OF STUDY PLAN

Pre-adolescent and AYA patients with newly diagnosed HR-ALL will have dietary and activity preferences assessed by a registered dietician (RD) and physical therapist (PT) at the start of induction.

Subjects will receive an individualized comprehensive dietary and physical activity plan. The RD and PT will devise a personalized dietary and activity intervention aimed at creating a minimum 10% caloric deficit each day (10% nutritional + exercise) throughout the four weeks of induction therapy. Adherence to the intervention will be assessed by the RD and PT at regular weekly intervals at routine clinic visits for chemotherapy and with home phone-calls between clinic visits. Home and hospital activity will also be recorded using a wearable electronic movement monitoring device (Fitbit ®) for all participants. A list of representative "menu" of possible activity interventions from which subjects may choose is provided as a separate Appendix. The primary efficacy of the intervention will be assessed in comparison to a recent historical control via determining the change in body fat percentage (and lean muscle) during induction as quantified by dual-energy x-ray absorptiometry (DXA). A key secondary aim will be the effectiveness of the intervention to reduce chemoresistance as evidenced by decreased prevalence of leukemia minimal residual disease (MRD) at the end of induction. MRD using multicolor flow cytometry is routinely assessed as a predictor of outcome in all patients with HR-ALL. Exploratory analyses will also examine biomarkers of the proposed mechanism including adiposity and intervention-related changes in leukemogenic signaling pathways, oxidative stress, and cellular metabolism. Parent- and subject-reported QOL assessments will consist of the PedsQL and Child and Adolescent Scale of Participation (CASP) surveys (see separate Appendix) and will be conducted pre- and post-induction and at two delayed time-points (mid-point of intensive chemotherapy [3 months from diagnosis] and at end of intensive chemotherapy phase [10 months from diagnosis] to assess the psychosocial benefits of the intervention.

6.2 TREATMENT PLAN

6.2.1 DIETARY INTERVENTION

The dietary intervention will be performed by an RD and is designed to achieve an at minimum ≥10% daily caloric deficit to prevent fat gain along with a moderate fat (20-25%), high protein (20-25%), and low glycemic index/high fiber carbohydrate (45-55%) nutritional plan to prevent loss of lean muscle mass loss and to maintain micronutrient intake. The subject's basal metabolic rate (BMR) will be calculated using the Schofield equation as per the World Health Organization recommendations (World Health Organization, Energy and Protein Requirements, Technical Report Series 724, 1985) with an activity factor of 1.3 ("for a well-nourished child at bedrest with mild to moderate stress") applied to better estimate the subject's resting energy expenditure (REE) from which to calculate the initial 10% caloric deficit goal. At the initial counseling session, the dietician and family will determine which dietary technique is most likely to lead to dietary adherence. Dietary management tools will incorporate the My Plate (USDA) and the Traffic Light Diet tools to help educate families regarding portion size and eating habits. The RD will use a menu of common foods that meet the intake goals above as well as help families choose "exchanges" on the menu to personalize the menu options to maximize adherence. During the initial

hospitalization, the RD will visit with the subject to assess caloric and nutrient intake using a 3-day food intake log, counsel subjects and their families on nutrition and eating habits, and instruct how to monitor food intake using a simplified log. If available, and if the family so desires, the option will be available for families to use their personal cell phone or digital camera to take pictures of meals (before consumption and after consumption) to email to the RD to help guide the dietary intervention.

During subsequent weekly outpatient chemotherapy clinic visits (or if the subject remains hospitalized), the RD will follow-up with families on their perceived adherence and obtain intermittent dietary intake via 24 hour diet histories. Between clinic visits, the RD will also contact the family to provide reinforcement/motivation, answer questions, and obtain interval dietary history if necessary. Specific dietary recommendations for foods/drinks, meals, and snacks will be adjusted weekly in discussion with families to meet the daily caloric deficit and goal diet as described. The caloric goals may also be adjusted ±5% depending on insufficient/excessive weight or body composition changes. At the end of the acute intervention, the RD will discuss with the subject and family their dietary status and sustainable healthy eating behaviors.

6.2.2 PHYSICAL ACTIVITY INTERVENTION

The physical activity intervention will be performed by a PT who regularly works with children on therapy for ALL as well as generally with pediatric oncology populations. The PT will meet the subject and family surrounding the time of initial diagnosis. The PT will assess at baseline the subject's usual activity level, choices/preferences, and available activities at home once discharged. A key component of this baseline assessment, and of beginning the exercise program during the initial hospitalization, will be education provided to subjects and their families to allay concerns over potential muscle weakness and/or fatigue and demonstrate with positive reinforcement how to exercise safely during leukemia therapy. During the assessment, the subject's "rate of perceived exertion" (RPE) will be assessed to gain insight into the subjects thresholds for exercise intensity.

A target of 200 minutes/week will be set for a combination of "moderate" cardiovascular exercise and resistance training (36) with progressive goals based on adherence and capacity. As per latest guidelines from the American Heart Association, this weekly target may be accomplished with a minimum of 30minutes/day or divided into 15-minute sessions over the course of the day with the goal of daily exercise. To quantify the prescribed "moderate" exercise, metabolic equivalents (METs) were assigned to a variety of exercise modes from which the subject may choose, which best suit their preference and home capabilities (Appendix I). While the goal exercise prescription in METs is uniform for the intervention, the PT will work with the family and subject to outline an individual path to meet that goal based on the subject's physical capabilities, preference, and home availability. METs will be converted to "points" and the subject will be able to choose from suggested exercise modes with the appropriate number of minutes to meet daily and weekly "point" goals. Subjects will be asked if there are any additional activities/exercises they would like to include. If so, these will be added and the "points" (METs) calculated for them. Participants and their parents will be asked to record the selected mode and number of minutes performed on a study log (or calendar) and weekly total scores will be tabulated (METs-

minutes). For patients who do not complete (or do not bring) the study log, adherence will be assessed by the PT at the time of visit via subject self-report of days meeting activity goals. The following scale will be used: 0% (<1day/week), 25% (1-2days/week), 50% (3-4days/week), 75% (5-6days/week), 100% (7days/week). Reported activity must meet 100% of that recommended for each qualifying day.
The exercise program will be progressive by nature such that the Daily Goal is increased each week depending on adherence, ability, and clinical condition.

All subjects will be provided a wearable electronic activity monitor (Fitbit®) to assist in recording home activity levels in minutes of activity; the Fitbit® has the important secondary benefit of providing visual reinforcement for the subject of their progress toward their Daily Goal as set by the study team.

6.2.3 MOTIVATIONAL INTERVIEWING (PROMOTION OF ADHERENCE TO INTERVENTION)

To facilitate adherence to the dietary and behavioral changes above, motivational interviewing (MI) techniques will be employed by the study team. MI is a patient-centered method for enhancing intrinsic motivation to change health behavior by exploring and resolving ambivalence through the use of empathetic, nonjudgmental, and supportive communication techniques (37). Numerous studies have illustrated the efficacy of MI as a promising strategy to encourage positive health behavior change (38), including promoting health behavior change and weight loss in nutrition and exercise interventions in children and adults (37, 39). Specifically, MI has been used to promote diet and exercise in breast cancer patients with some success (41).

6.2.4 INTEGRATION OF INTERVENTION INTO ALL THERAPY

While induction chemotherapy for pediatric ALL is a highly morbid and overwhelming time, the study team has significant experience working both with this specific population as well as other populations with high morbidity. While lifestyle changes in general are difficult to achieve, short-term changes are generally more successful and patients and families in general are more receptive to short-term achievable goals.

In this context, the 28 day intervention proposed here is purposefully designed to naturally integrate into the four week induction phase beginning with the start of systemic chemotherapy. This phase routinely includes an initial hospitalization followed by weekly clinic visits with the treating provider for delivery of chemotherapy and evaluation of toxicity. The study intervention and assessments are therefore formulated around this routine clinical schedule.

Subjects will be enrolled surrounding the time of initial diagnosis within 24 hours of starting systemic chemotherapy. Children are routinely hospitalized for a minimum of four days from the start of systemic chemotherapy. During this time, they will have their baseline DXA scan (within 96 hours from start of systemic chemotherapy), the initial PT and RD assessments, and start with the supervised activity intervention and diet intervention. Bedside nursing will be available to provide reinforcement during that time. Following anticipated discharge, the subjects will be assessed at each weekly clinic visit to have their diet and activity interventions monitored and adjusted as needed and also to receive

education/motivation from the psychosocial team. At the final clinic visit at the end of induction, subjects will receive the post-intervention assessments along with additional motivation/education. Subjects will then continue on chemotherapy per routine care with ~8-9 additional months of intensive chemotherapy; subjects will receive PT, RD, and QOL assessments midway at the start of "interim maintenance" and again at the final time-point at the start of the low-intensity maintenance phase. These follow-up visits will help gauge whether the effect of the intervention and education extinguished or persisted during the intervening post-intervention months.

6.3 SUBJECT REMUNERATION

While no payment is provided to subjects for participation, a Fitbit© will be provided to participants, as part of the study assessments as indicated in the schema and described further below. At the conclusion of the study's follow-up portion, the subjects (or parent/guardian if the subject is <13 years of age) will be permitted to keep the Fitbit should they wish to do so.

7.0 MODIFICATIONS OF INTERVENTION FOR TOXICITY

7.1 MODIFICATION OF ACTIVITY INTERVENTION

Instances may arise throughout the course of induction therapy in which subjects may not be able to adhere to the prescribed activity intervention due to complications from leukemia treatment. Initially, attempts will be made by the PT to lower the intensity of the intervention until complications subside. If treatment-toxicity is persistent or severe (i.e. subject in the PICU), the activity intervention will be suspended until the subject is deemed to be able to resume the intervention by the PT in consultation with the subject's treatment team.

7.2 MODIFICATION OF DIETARY INTERVENTION

Similarly, a subject may not be able to adhere to the nutrition intervention for reasons such as, nausea/emesis or the treatment team determining the subject cannot receive liquids or food by mouth (NPO). In such instances, the study team will continue to track all data at specified time-points and the registered dietician will re-assess nutritional caloric goals. Moreover, for subjects at lower BMI percentiles, despite the anticipated body fat gain, should the BMI percentile decrease to <5th percentile, the subject will come off-therapy as per Section 12.1.

8.0 SUPPORTIVE CARE GUIDELINES

All supportive care should be provided as per standard of care and institutional guidelines. No specific precautions are required for patients on study.

9.0 REQUIRED OBSERVATIONS

Please see "experimental schema" in study preamble for overview of treatment and required observations.

9.1 REQUIRED OBSERVATIONS

"At Diagnosis" blood samples should be collected before or in closest proximity as possible to starting systemic chemotherapy (steroid pre-treatment, steroid prophase, or intrathecal therapy may have already been given), but all samples **must be collected before the start of the activity/nutrition intervention and prior to the end of chemotherapy day 4**

The DXA scan should be done in closest proximity to diagnosis as is feasible, but **must be done** within **96 hours from the beginning of systemic chemotherapy** and ideally before the start of the activity/nutrition intervention. The timing of the DXA scan in relation to chemotherapy and the intervention will be recorded.

STUDY MEASURE		Diagnosis (Day 1)	Day 8	Day 15	Day 22	End Induction (Day 29)	Start IM#1	Start Maint
Patient History	Clinical History[1]*	X	X	X	X	X	X	X
Anthropo-metrics	Height/Weight*	X	X	X	X	X	X	X
	Tricep skin folds	X	X	X	X	X	X	X
	Waist to hip ratio	X	X	X	X	X	X	X
Clinical Assessments	RD Assessment-3 day food log	X				X		
	RD Assessment-24 hr recall	X	X	X	X	X	X	X
	PT Assessment-Complete BOT2	X				X		
	PT Assessment-BOT2 –Brief		X	X	X		X	X
	Fitbit Tracker	Continuous from time of study entry until study end						
Laboratory Tests (blood)[2]	Liver function tests[3*] (AST/ALT/Bili)	X	X	X	X	X		
	Lipid Panel	X				X	X	X
	Mittelman Labs	X				X	X	X
	Peripheral blood leukemia blasts[4]	X						
	Pregnancy Test*	X				X		
Pathology Tests	Bone Marrow Aspirate[5]*	X				X		
	Biopsy Marrow Biopsy[5]	X*				X		

Radiology Tests	DXA Scan	X				X[6]		
Survey Instruments[7]	PedsQL - Core	X				X	X	X
	PedsQL - Fatigue	X				X	X	X
	CASP	X				X	X	X

*Indicates test per Standard of Care (SOC). [1] Clinical History includes any time NPO, any use of nasogastrointestinal (NG) or nasojejunal (NJ) nutrition, any parenteral nutrition, any surgeries, any ICU admissions, Grade 3 or 4 hepatic or pancreatic toxicity, presence of osteonecrosis or fracture. [2]Research laboratories to include IGF-1 and obesity-related interleukins/signaling factors, leptin, adiponectin. Peripheral blood will not be collected in patients who are Jehovah Witness or with a medical contraindication. [3] Will record if collected routinely per SOC. Each visit ±3 days. End of induction includes any time prior to start of Consolidation phase. If Grade 3 hepatic toxicity during induction, will record values with date of resolution through start of IM#1 (<grade 2). [4]To be collected in those with a circulating absolute blast count ≥500/uL. [5]Extra aspirate for research will be collected as per below only if sufficient specimen is available; only specimens from bone marrow biopsies processed in saline will be collected for study.[6] End of induction scan to be done between days 29 and 36 of therapy in as close proximity to day 29 as possible and prior to any subsequent systemic chemotherapy. [7]Available in Spanish and English; if subject does not speak either, will be administered in an assisted manner using in-person or phone-based medical interpreters.

9.2 RADIOLOGY

For those subjects who are female and of reproductive age, in addition to a pregnancy test at study entry as per routine care prior to chemotherapy, pregnancy will be assessed as per institutional guidelines at each site prior to any radiological tests. The results of these tests will be confidential.

9.3 BONE MARROW ASPIRATE & BIOPSY

As per the preceding CHLA ALL Obesity Environment & Microenvironment Study #2, subjects on study may require extra bone marrow aspirate and biopsy for study purposes. The bone marrow aspirates will be collected during the same anesthesia and procedure being done for clinical care purposes and will be collected after the clinical specimen is obtained. If there is insufficient specimen available, there will be no additional aspirates (needle punctures) performed for study purposes only and no bone marrow leukemia cells will be expected from that time-point for study. If a routine bone marrow biopsy at diagnosis was performed with sufficient extra specimen, a piece will be collected for study purposes. Subjects undergoing bone marrow aspiration at end of induction for clinical purposes will also require a single additional research-only bone marrow biopsy to be performed at the same time. For sites that do not (or cannot) collect bone marrow biopsies in saline, marrow biopsies will not be collected for this study.

Similarly, bone marrow biopsies not collected in saline (for any reason) will not be obtained for this study as it precludes analysis of the marrow fat.

9.4 EXTRA SAMPLE

Any extra blood or bone marrow specimens collected at time of diagnosis or later while on this study, which is not needed for clinical purposes by the laboratory or pathology department may be used for further research purposes. Blood may be used for measurements of other related tests including but not limited to amino acids, cytokines, adipose tissue hormones, and/or collection of viable leukemia cells. Extra bone marrow aspirate/biopsy material may be used for examination, culture and studies to investigate cells type and functions. All testing will be done in the context of further investigating the relationships between bone marrow microenvironment, nutrition, osteoblasts, adipocytes and leukemia.

9.5 LABORATORY INFORMATION

Serum levels of standard lipid panel and all other tests performed per standard of care will be performed by the hospital clinical laboratories. Blasts, marrow adipocytes, and serum collected at CHLA for the assessment of obesity-associated laboratories will be stored at The Saban Research Institute until being batch shipped to Dr. Mittelman's laboratory where they will be assayed in a batched manner.

Samples collected from patients enrolled at other sites will be stored at that site and shipped directly to the Dr. Mittelman's Laboratory (i.e. these will not be received at CHLA).

Serum is to be aliquoted in 1ml cryovials and FROZEN at -80C. Serum is to be labeled with (1) Study ID, (2) Date, and (3) Study visit.

Coded samples will be shipped to the laboratory of Dr Mittelman:

Steven Mittelman, M.D., Ph.D.
David Geffen School of Medicine, UCLA
10833 Le Conte Ave, MDCC 22-331
Los Angeles, CA 90095

In brief, subjects will have central catheters accessed (if applicable) by heme/onc nursing per routine clinical care. Phlebotomy if necessary will be performed by heme/onc clinical nursing or hospital-based clinical laboratory. Blood draws will be coordinated with routine collection where-ever possible. It is recommended that study bags be provided to nursing prior to study visits that will contain all necessary specimen tubes and instruction regarding volumes to be drawn. Labels and/or instructions will be included regarding specimen distribution and specimen processing. At CHLA, for reference (and if study bags unavailable), please see Appendix I which contains all relevant details.

10.0 RADIOLOGY SAFETY INFORMATION

Radiological studies will expose subjects to small amounts of radiation. Subjects will have quantification of body fat content by DXA. This type of scan is necessary as it provides complementary information and is the "gold standard" method to quantify body fat.

Each DXA examination exposes the subjects to less radiation than a single standard chest x-ray (DXA = ~1/6 a standard chest x-ray). DXA confers a radiation total effective dose equivalent (TEDE) of ~0.5 mREM of radiation per scan. This is a total study exposure of ~1 mREM for subjects (2 DXA scans). The critical organ exposed is the gonads; DXA contributes a total study exposure of 0.24 mREM to gonads in subjects. The total radiation exposure from the DXA scans is minimal and well beneath the 100 mREM upper limit considered to be "minimal risk" by the radiation safety committee.

In common terminology, everyone receives a small amount of unavoidable radiation each year named "background radiation." Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. Participation on this research study gives the subject the equivalent of about **1 extra day** of this natural radiation **and is less than that of a single standard chest x-ray.**

11.0 MISCELLANEOUS PATIENTS RISKS

11.1 BLOOD COLLECTION

Subjects with central venous catheters will have extra blood collected for the study when there catheters are being accessed and blood drawn for clinical purposes. As per above, patients with religious (Jehovah Witness) or medical contraindications will not have blood collected. The collection of extra blood for study will prolong the procedure for less than 2 minutes and will not cause any significant discomfort. Subjects without central venous catheters will require venipuncture at each visit (using a needle to draw blood from a vein). This may cause mild pain or a bruise at the site where the blood is to be collected. Occasionally, a person may feel faint during the time of blood collection. The risk for infection is very rare since only sterile one-time equipment will be used. If possible, sample collection will be coordinated with venipuncture for clinical purposes.

11.2 BONE MARROW ASPIRATE & BIOPSY

All research procedures will be coordinated with clinical bone marrow aspirates and biopsies. If there is insufficient specimen available from the bone marrow aspirate, there will be no additional aspirates performed for study purposes only. As such, there is minimal additional risk to this procedure. The research-only biopsy at the end of induction will be coordinated with the routine bone marrow aspirate; the biopsy will be obtained per standard practice using the same skin puncture with minimal prolongation of anesthesia (typically less than 3 minutes) with minimal additional post-operative discomfort due to the addition of the biopsy to the aspirate. Post-operative care routinely includes assessments of discomfort and the clinical care teams will assist in managing this as needed.

11.3 POTENTIAL RISKS OF INTERVENTION

We do not anticipate any risks directly due to the dietary intervention. Subjects may be at risk for syncope, falling and injury during the activity intervention. The PT will design an activity intervention for each subject that will aim to reduce the risk of fall and injury in patients that experience or develop minor difficulties balancing. In-hospital activity interventions will be properly supervised by a PT with vast experience handling pediatric cancer patients undergoing therapy. The potential risks of home-based

activities and methods for reducing risks will be discussed with patients and their families. Changes in weight and body composition are being carefully monitored by both a RD and PT throughout the intervention. Subjects that are unable to adhere to the dietary and/or activity intervention may be at risk for psychological distress (i.e. depression, anxiety, etc.). The treatment team will work to proactively address these risks in each patient through positive discussion and adjustment of the intervention if necessary. Additionally, each patient may be at risk for psychological distress following the introspective nature of the QOL assessment. Psychological distress from any facet of the intervention will be monitored by the treatment team and referred to the psychosocial team if necessary.

11.4 OTHER RISKS

As described above, there is a risk of radiation exposure from DXA scans to pregnant subjects. This risk will be minimized through routine procedures for women of child-bearing age undergoing chemotherapy including a pregnancy test at start of chemotherapy, tests per hospital policy prior to radiology exams, and guidance for adequate birth control or abstinence provided per routine by the primary treatment team. Confidentiality will be maintained to the standards set by Good Clinical Practice including no identification by name in any published research. Despite best efforts, there remains a risk for "breach of confidentiality" of the collected information.

12.0 CRITERIA FOR REMOVAL FROM THERAPY AND OFF-STUDY CRITERIA

12.1 OFF-THERAPY CRITERIA

1. Continuation of the intervention is determined by physician judgment to not be in the best interest of the patient
2. Subject refuses study interventions (but desires to continue with study observations)
3. Subject's BMI decreases to <5th percentile for age- and sex- (or <18.5 for those >20 years)

Subjects who are off study therapy will continue to be followed with collection of laboratory, radiographic, survey, and assessment data unless they meet the criteria for off study (see below).

For off-therapy patients, by family request and/or in response to questions during the assessments, routine clinical guidance for healthy diet and exercise will be provided by the PT and RD.

12.2 OFF-STUDY CRITERIA

1. Death
2. Relapse of Leukemia
3. Change in treatment plan during induction (i.e. during the study intervention) that no longer meets initial eligibility requirements
4. Lost to follow-up
5. Subject withdrawal of consent
6. Study closure

Study Closure: The study will remain open for follow-up only for a period of 5 years from the last day of follow-up for the final subject. During this time, there will be no study-specific visits or tests, but study personnel may contact patients in clinic or via telephone to obtain information relevant to patient health and diet and activity habits, and/or other relevant information that may become apparent throughout the course of the study, including but not limited to interventions performed by other care providers, survival, or relapse. For this purpose, study records and coding information will be maintained in a confidential database as below until study closure.

13.0 STATISTICAL CONSIDERATIONS AND EVALUATION CRITERIA

13.1 SAMPLE SIZE AND STUDY DURATION

Based on available data over a recent 3-year period (2012-2014), we predict at least 43-45 subjects ≥10 years of age with HR-ALL patients will be eligible for enrollment during the three year study. We anticipate >85% of subjects to be enrolled & evaluable for the primary and secondary aim surrounding the Day 29 time-point, for an effective sample size of at least 36 subjects. As of AMD03, additional site(s) were added to gain experience with the study intervention at outside institutions; there is no change to the target study accrual goal of 36 evaluable subjects.

As subjects historically gain body fat during induction irrespective of starting body composition (i.e. both those lean and those overweight/obese gain body fat), we will enroll a goal of 18 overweight/obese and 18 lean subjects on the study to evaluate for an overall effect of the intervention, as well as a differential effect in those "lean" by BMI percentile. We will continuously monitor accrual by weight category with a minimum final target accrual of 14 overweight/obese and 22 lean subjects (40/60) which, as below, preserves our ability to detect an effect on body fat and on the key secondary aim of MRD. For assessment of the delayed endpoints, we expect that 80% of the initial cohort will additionally be evaluable for secondary the aims at the final pre-start of maintenance time-point (due to treatment-related morbidity/mortality/lost-to-follow-up).

13.2 PRIMARY ENDPOINT EVALUATION

The primary endpoint for efficacy is a reduction in gain of body fat percent (per DXA) from diagnosis to the end of induction. From data on 36 patients from the historical cohort at CHLA with DXA scans pre and post induction, there was a significant average fat gain during induction therapy of 5.5±3.3 percent (mean ± s.d.), $p<0.001$. Based on a two-sample (36 historical, 36 present study) two-sided t-test with 5% Type I error, there will be at least 90% power to detect a 2.5 percentage point reduction in change in body fat as a result of intervention (e.g. from gain of 5.5 to a gain of 3.0%). Hence, this study has sufficient power to detect subtle, achievable effects on body fat during induction, and will with certainty detect stabilization of or a decrease in body fat during induction.

13.3 SECONDARY ENDPOINTS Evaluation

To compare the rate of leukemia "positive" minimal residual disease (MRD) in the bone marrow at end of induction (≥0.01% mononuclear cells) in those who received the intervention as compared to historical controls.

The key secondary endpoint for efficacy is whether or not the bone marrow is "positive" for MRD at the end of induction (using the COG definition of ≥0.01% mononuclear cells). From the retrospective study at CHLA of B-precursor ALL/obesity and end-induction MRD, 69 patients in the cohort had HR-ALL over the age of 10 at diagnosis. Of these, 53% of those overweight or obese (n=30) were MRD positive at the end of induction as compared to only 26% of those lean at diagnosis (n=39). Using this cohort as the historical comparison group, for the overweight/obese subset only, this study will have approximately 80% power to detect a reduction in the MRD positive rate to approximately that of the historical lean group (i.e from 53% to 24%) based on a two-sample, one-sided test of proportions with a Type I error of 0.10 (as a commonly used "go/no go" threshold to continue to Phase III trials). For the overall cohort, again in comparison to the historical cohort (MRD+ 38%, n=26/69) using a similar two-sample, one-sided test of proportions, the study will have the ability at ~80% power to detect a decrease in MRD by 20%. The study will therefore provide data on the potential reduction in the MRD positive rate that can be expected in preparation for the subsequent randomized Phase III trial for efficacy. These analyses will be adjusted for risk group, age, and other factors as appropriate and also compared to external published rates for MRD positivity.

To assess adherence to, and feasibility of, implementing a personalized and comprehensive dietary and exercise intervention during the first month of intensive chemotherapy

This endpoint will be reported as the proportion of study subjects who adhere to proposed dietary and activity interventions. A threshold of 80% of RD and PT visits (combined, RD only, PT only) completed will determine feasibility of incorporating the intervention itself into induction therapy. Adherence to each component of the intervention will be further assessed using a threshold of 75% MET-minutes prescribed/completed and 75% of dietary adherence prescribed/actual intake (overall, and to each macronutrient group). Further exploratory analysis will examine which sets of activities and dietary recommendations afforded the greatest level of adherence and any trends toward adherence by age, sex, race, and/or ethnicity.

13.4 EXPLORATORY ENDPOINTS EVALUATION

To evaluate persistence or extinguishing of this effect during continued dose-intensive phases of chemotherapy

Reported continued adherence to activity and dietary recommendations will be evaluated by the RD and PT as per last prescribed or recommended from the intervention versus actual minutes/dietary intake at the delayed time-points of start of Interim Maintenance (~+3 months) and start of Maintenance (~+10 months). Activity and dietary intake patterns will also be compared to baseline at-diagnosis levels. Similar exploratory analysis will examine the effect of age, sex, race, and/or ethnicity.

To characterize the direct impact as compared to baseline of the intervention on self- and family- reported quality of life (QOL) outcomes including fatigue, mood, social interaction, and cognitive impairment reported via the PedsQL questionnaire and Child and Adolescent Scale of Participation (CASP) following the induction phase and serially during dose-intensive phases of chemotherapy

The PEDSQL questionnaire returns a QOL score between 0-100 for each patient at each time-point. The CASP is scored as a percentage and then normalized to a 100 point score. Differences during therapy will be compared using a two-sided, paired t-test during induction (the intervention) and using repeated measures analysis for all four time-points.

To quantify the effect of adiposity at diagnosis on the activity of leukemogenic JAK2/STAT3, PIK3K/AKT/mTOR, MAPK/ERK, and other signaling pathways in leukemia cells as determined by kinase phosphorylation

Differences in levels of expression of the pathways will be analyzed according to body fat percentage (adiposity) using a two-sided, two-sample t-test for the different pathways as well visually for overall trends in related pathways.

To quantify the effect of adiposity and of the intervention on the metabolic activity of leukemia blasts and of adipocytes as assessed by IGF-1, other obesity-associated cytokine signaling pathways, adiponectin, leptin, free fatty acid synthesis and metabolism, and levels oxidative stress.

Exploratory analyses using similar t-tests will be performed to explore the effects of adiposity at diagnosis on adipokines, obesity-associated cytokines, oxidative stress, and measures of cellular metabolism. The effect of the intervention on oxidative stress and free fatty acid synthesis will be analyzed using paired t-tests for pre/post intervention and compared to samples from the historical cohort.

14.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) data collection and reporting are required as part of every clinical trial to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a prescribed manner at scheduled times during the trial.

Induction chemotherapy has many associated toxicities due to the intensity of regimen, and these will be monitored per routine care by the treatment team and/or by the appropriate research team if the subject is enrolled on a concurrent therapeutic research study.

We will not record non-targeted toxicities (those described in clinical history Section 9.1) due to the underlying leukemia or treatment regimen.

As this trial consists of behavioral interventions (diet and exercise) that are within the scope of standard of care for patients, we will ONLY collect AE's that occur *during* or *immediately* following the exercise activities. If this should occur, the AE will be reported to the local IRB and the coordinating IRB (CHLA).

For an AE that occurs as above, we will record and report using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (CTCAE) available for download at http://ctep.cancer.gov.

All reporting of adverse events must include:

- severity (grade) of the event
- duration of the event
- attribution to the study (i.e. how the event is related to the study).
- whether hospitalization was necessary (or prolonged) for subjects

Categories of attribution in order of increasing likelihood are:

- Unrelated
- Unlikely
- Possible
- Probable
- Definite

All adverse events will be labeled "unexpected" for this behavioral study intervention.

14.1 EXPEDITED REPORTING OF ADVERSE EVENTS

As a behavioral intervention that does not pose more than minimal risk to the subject, expedited reporting will only be required in the case:

Toxicities that occur during this protocol-specified activity (as described above) and cause or prolong hospitalization will be reported in an expedited manner to the IRB within 5 business days.

Toxicities that are ≥ Grade 4 and occur during the protocol-specified activity (as described above) will be reported in an expedited manner to the IRB within 5 business days.

15.0 RECORDS AND REPORTING

Research records will be maintained through paper study-specific case reporting forms (CRF). Research records for this study will be maintained in locked cabinets in the Clinical Trials Office (CTO) or institutional research offices accessible only to the investigators and study team. The master list linking subjects to their unique identifier will be kept in the regulatory binder locked in the CTO office and in a password-protected database. Regulatory binder and CRFs will be maintained primarily by the research coordinator with assistance from the PIs/investigators as needed.

Study results will be entered by each site directly into the secure REDCap database maintained by USC/SC-CTSI. At conclusion of the treatment portion of the study, screening logs with coded identifiers only will be provided from each site to enable assessment of selection bias (e.g. CONSORT diagream). The database will then be downloaded by the study PI for potential further secondary analysis and follow-up as indicated in Section 13.2 ("Study Closure"). The database will remain under unique password-protection and will be remain strictly confidential. At the conclusion of the prescribed 5-year follow-up period (final study closure), all identifying information will be destroyed and the database will be preserved in a password-protected completely de-identified format for a minimum of six years as per CCI requirements at which time it will be destroyed.

16.0 DATA AND SAFETY MONITORING PLAN

The Principal Investigators or designees will be available to answer questions of patients on the research protocol. As the study intervention constitutes a standard-of-care behavioral intervention only, data and safety monitoring for all patients enrolled on the study will be conducted by the study committee on an ongoing basis while the study is open.

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