A DOUBLE-BLIND STUDY OF NUTRITIONAL INTERVENTION FOR THE TREATMENT OF CANCER CACHEXIA USING JUVEN® NUTRITIONAL SUPPLEMENT

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A DOUBLE-BLIND STUDY OF NUTRITIONAL INTERVENTION FOR THE TREATMENT OF CANCER CACHEXIA USING JUVEN® NUTRITIONAL SUPPLEMENT

SCHEMA

S  Primary Disease Site  R  Concurrent Chemotherapy
1. Lung  1. No
2. All others  2. Yes

T  Evidence of Metastases  O  Degree of Weight Loss
1. No  1. 2-5%
2. Yes  2. 6-10%

F  Juven® supplement a b.i.d. for 8 weeks  I  Z
Juven® supplement a b.i.d. for 8 weeks  Non-Juven® supplement b b.i.d. for 8 weeks

E  a. Juven® supplement: arginine (free-base), 14 gm; glutamine, 14 gm; HMB (calcium salt), 3 gm
b. Non-Juven® supplement: l-alanine, 7.72 gm; glycine, 4.28 gm; l-serine, 2.96 gm; l-glutamic acid, 1.23 gm; gelatin, 30.52 g

Eligibility: (See Section 3.0 for details) [6/11/03]
- Patients with histologic/cytologic diagnosis of cancer (Stages III or IV) at presentation or patients with any stage at presentation and with current metastatic disease; measurable disease need not be present.
- Patients with any solid tumors (including lymphomas with no leukemic aspect), except brain tumors (primary or metastatic), are eligible.
- Weight loss ≥ 2% and ≤ 10% (relative to the patient’s current weight) within the previous three-month period
- Zubrod 0-2
- Life expectancy ≥ 3 months
- At least three weeks since major surgery; at least 1 week since minor surgery
- Chemotherapy and/or radiation therapy during treatment are acceptable.
- No current intestinal obstruction, metabolic disorder, hypercalcemia, enteric fistula, or uncontrolled infections
- No persistent moderate or severe peripheral edema, ascites, or uncontrolled congestive heart failure; no other serious medical illness
- No concurrent steroids, dronabinol, megestrol acetate; no use of omega 3 fatty acids (such as ProSure™, Ross Laboratories); patients on intermittent dexamethasone during chemotherapy are eligible.
- Patients currently receiving parenteral feedings are ineligible; patients receiving enteral feedings through feeding tubes are eligible.
- Women who are presently pregnant or nursing are ineligible.
- Pretreatment evaluations must be completed as specified in Section 4.0.
- Patients must sign a study-specific consent form prior to study entry.

Required Sample Size: 468
Institution #
RTOG 0122
Case #

ELIGIBILITY CHECKLIST (6/11/03)

(continued on page 2)

1. Did the patient have histologic/cytologic diagnosis of cancer, Stages III or IV at presentation or any stage at presentation with current metastatic disease? _____(Y)

2. Does patient present with solid tumor (including lymphomas with no leukemic aspect), except brain tumors (primary or metastatic)? _____(Y)

3. Has the patient demonstrated a weight loss of at least 2% and not more than 10% (relative to the patient’s current weight) in the previous three months? _____(0-2)

4. What is the Zubrod Performance Status? _____(Y)

5. Does the patient have an expected survival of three months or greater? _____(Y)

6. Has it been at least three weeks since major surgery; at least one week since minor surgery? _____(Y)

7. Were pretreatment evaluations completed per Section 4.0 of the protocol? _____(Y)

8. Has the Schwartz Cancer Fatigue Scale (SCFS) and the Spitzer Quality of Life Index (SQLI) been completed? _____(Y)

9. Does the patient have any of the following:
   - Current intestinal obstruction, metabolic disorder, hypercalcemia, enteric fistula, or uncontrolled infections?
   - Persistent moderate or severe peripheral edema, ascites, uncontrolled congestive heart failure, or other serious medical illness? _____(N)

10. Is the patient currently taking known appetite stimulants such as megestrol acetate, dexamethasone (corticosteroid), or dronabinol? (Patients on intermittent dexamethasone during chemotherapy are eligible.) _____(N)

11. Is the patient currently using omega 3 fatty acids (such as ProSure™) or their congeners? _____(N)

12. Is the patient currently receiving parenteral feedings? _____(N)

13. Is the patient presently pregnant or nursing? _____(N)

14. Has the patient signed a study-specific consent form? _____(Y)

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case? _____________

2. Has the Eligibility Checklist (above) been completed? ______(Y) (continued on page 2)
3. Is the patient eligible for this study?

4. Date the study-specific Consent Form was signed? *(Must be prior to study entry)*

5. Patient’s Initials *(Last, First)*

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Race

10. Ethnic Category *(Hispanic or Latino; Not Hispanic or Latino)*

11. Gender

12. Patient’s Country of Residence

13. Zip Code

14. Patient’s Insurance Status

15. Will any component of the patient’s care be given at a military or VA facility?

16. Is there concurrent chemotherapy?

17. Is there any evidence of metastases?

18. Will the patient have access to bioimpedance measurements?

19. Will the patient have access to BOD POD® measurements?

20. Specify primary site of disease *(lung or other)*.

21. Specify percent of weight loss *(relative to the patient’s current weight)* over the last 3 months *(2-5% or 6-10%).*

22. Treatment Start Date

**BLINDED**

23. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _______________________________  Date ____________________
INTRODUCTION

1.1 Cancer Cachexia: Tumor Biology Issues

1.1.1 Prevalence
The true incidence of the cachexia seen in advanced malignancy, when the elements of anorexia, weakness, weight loss, and hypophagia are considered, approaches 100% in most series.\(^1\) The presence or absence of weight loss predicts survival in patients receiving cancer therapy.\(^2\) This phenomenon is independent of actual tumor volume, and it is known that in both experimental animal systems and in humans, different tumor types have varying abilities to cause cachexia. This is particularly true with lung cancer (both small cell and non-small cell types), pancreatic, gastric, and cervical cancers, and end stage leukemia, in which weight loss and cachexia are common clinical occurrences. It is less commonly seen in patients with breast, colon, or prostate cancers.

1.1.2 Cancer Cachexia and Protein Metabolism
The derangements in carbohydrate and lipid metabolism seen in cachexia are poorly understood, as is the mechanism behind skeletal muscle mass depletion.\(^1\) It is the loss of protein that appears to have the most significant impact on survival. Cancer patients lose the normal response to weight loss of preferential use of adipose stores and decreased energy expenditure, as seen in chronic fasting or in starvation models. The protein wasting seen in advanced cancer is the result of complex changes in nitrogen balance and inappropriate turnover of whole body protein stores. Tumors appear to preferentially utilize certain amino acids and obtain them at the expense of the host, independent of nutritional or caloric intake. This may be related to circulating levels of prostaglandin PGE-2, to tumor products, or to host interactions related to production of cytokines such as TNF\(\alpha\), IFN\(\gamma\), IL-6, or proteoglycan 24K.

1.2 Amino Acid Regulation of Proteolysis

1.2.1 \(\beta\)-hydroxy \(\beta\)-methyl butyrate (HMB):
The proposal to use \(\beta\)-hydroxy \(\beta\)-methyl butyrate (HMB) to suppress proteolysis originates in the observations that the amino acid leucine has protein-sparing characteristics.\(^3\)-\(^6\) HMB is hypothesized to be the bioactive component of leucine that regulates muscle proteolysis.

1.2.1.1 Origins of HMB
Nearly 80% of the essential amino acid leucine is used for protein synthesis while the remainder is converted to the \(\alpha\)-ketoacid (\(\alpha\)-ketoisocaproate, KIC). KIC can either be reconverted to leucine or catabolized. The major route of KIC metabolism (and indirectly leucine) is through oxidation to isovaleryl-CoA (IVA-CoA) by the mitochondrial enzyme KIC-dehydrogenase. In the second pathway, KIC can be oxidized to HMB by the cytosolic enzyme KIC-dioxygenase. This enzyme requires iron and molecular \(O_2\) for its action. Approximately 5% of leucine oxidation proceeds via this second pathway.\(^7\) Studies conducted by Nissen et al. in pigs indicate that 100% of circulating HMB is derived from leucine.\(^7\) In certain situations in humans and rats, however, it has been shown that HMB can be derived from hydration of \(\beta\)-methyl-crotonyl-CoA (MC-CoA). In cases of severe biotin deficiencies\(^8\)-\(^12\) and in humans with genetic defects in leucine metabolism\(^13\)-\(^18\), MC-CoA concentrations can increase which result in increased production of HMB. Increased urine HMB has been noted in ketoacidosis.\(^19\) This increase in urine HMB is likely the result of the increase in plasma leucine and KIC concentrations, which force more KIC to be oxidized by the oxygenase pathway.

1.2.1.2 Metabolism of HMB in Mammals
HMB appears to have two fates. The first is simple urine excretion. After ingestion of HMB, the urine concentration of HMB, increases, resulting in approximately 20-50% of the HMB dosage being lost in the urine in humans, sheep, and pigs.\(^20\) A second pathway is the activation of HMB to HMB-CoA,21-29 The enzyme that carries out this activation has not yet been described, and it is quite likely that this is a non-specific side reaction of an enzyme not particular to the HMB pathway. Once converted to HMB-CoA, further metabolism may occur via the crotonase enzyme dehydrating HMB-CoA to MC-CoA. A pathway of direct conversion of HMB-CoA to HMG-CoA may also exist.\(^30\)

1.2.2 Glutamine
Glutamine is essential for the metabolism of rapidly turning over cells such as lymphocytes, and enterocytes.\(^31\) Glutaminolysis (glutamine degradation) provides both nitrogen and carbon precursors for the synthesis of macromolecules (e.g., purines and pyrimidines used for DNA and RNA synthesis) and as supplying energy.\(^32\) Clinical conditions associated with excessive cellular turnover, as occurs with tumor progression, are characterized by excessive depletion of muscle glutamine stores and with depression of natural killer (NK) cell activity. In vitro studies support a dependence of NK cell activity on glutamine and glutathione concentrations in the incubation media.\(^33\) Additional evidence indicates that oral
glutamine supplementation, through support of the host glutamine stores and glutathione production, leads to decreased tumor growth by enhancing NK cell activity. This immune function enhancement, resulting from glutamine supplementation, is attributed to enhanced synthesis of lymphocytes. In the absence of appropriate exogenous sources, the requirements for glutamine must be met from an endogenous source. Skeletal muscle synthesizes, stores, and releases the majority of glutamine in the body. Excessive demands on glutamine from high utilization leads to significant muscle wasting. These studies lead to the hypothesis that exogenous supplementation of glutamine stores may prevent the excessive wasting that occurs during cancer cachexia. We estimate that the glutamine requirements in this patient population may be near 10-14 grams per day.

1.2.3 Arginine

Several studies have presented evidence for an important role for arginine in modulating the immune response, particularly lymphocyte proliferation. Beneficial effects for oral supplementation have been observed in the elderly, with marked improvements in immune function and wound healing. Arginine has also been demonstrated to enhance the immune response of patients with malignancy. Based on the in vitro requirements of arginine by lymphocytes and skeletal muscle, we estimate that the additional daily requirements of arginine in the newly diagnosed asymptomatic cancer patient to be approximately 10-12 grams per day.

1.2.4 Previous Studies

1.2.4.1 Animal Studies with HMB

Numerous animal studies have been carried out with HMB. These studies have shown that HMB has important physiological effects in animals including immune stimulation and disease prevention. Effects on growth and muscle metabolism have also been noted, but these effects vary with species. Studies of the effects of HMB on in vitro protein synthesis and proteolysis in isolated rat muscle found that HMB inhibited protein breakdown, with minimal effect on protein synthesis. Proteolysis was measured by the efflux of tyrosine from muscle and synthesis was determined by measuring the uptake of labeled tyrosine. These data indicate that HMB is a potent inhibitor of muscle proteolysis in vitro, and we have recently confirmed these findings in humans. (see below).

1.2.4.2 Effect of HMB in Exercising Humans

In a study performed at Iowa State University, Ca-HMB was supplemented to college-age male subjects undergoing the stress of weight training. Forty-five untrained subjects were assigned to 0, 1.5, or 3.0 g of Ca-HMB split into two doses per day. Half of the subjects ate diets containing ~117 g of protein per day, and the other half ate diets containing ~160 g of protein per day. After a one-week adjustment period in which body composition (TOBEC) and basal blood and urine samples were collected, all subjects underwent moderate strength training three times weekly for three weeks. At the end of the three-week study a strength test was given and the gain in strength calculated. At the end of each week, blood and urine were collected for analysis. Two 24-hour urine collections were taken each week for 3 methyl-histidine (3-MH, an index of total body proteolysis) and nitrogen balances. Subjects were fed a meat-free diet the day prior to and throughout the urine collections. At the end of the study, each subject had a repeat TOBEC to measure body composition. Results: As expected, the heavy weight lifting regime produced a large amount of muscle damage after the first week. Plasma creatine phosphokinase (CPK) levels rose from 200 to more than 15,000 U/ml in the control group. Ca-HMB attenuated the rise in CPK levels in the group receiving the 3.0 g/day dose (from 15,868 to 8,311 U/ml, p<0.001). Urine 3-MH (also an indicator of muscle breakdown) decreased in a linear manner with Ca-HMB supplementation (4%, 3.5%, and 2% breakdown per day expressed as % lean body mass catabolized per day in 0, 1.5, and 3.0 g/d, respectively). These data suggest that Ca-HMB markedly decreased muscle damage during resistance exercise as evidenced by less leakage of CPK from muscle and lower muscle proteolysis. There was also an associated increase in lean gain (0.41, 0.80 and 1.21 kg in 0, 1.5, and 3.0 g/d, respectively). These were accompanied by a linear increase in strength with Ca-HMB supplementation (14%, 22%, and 26% increase in 0, 1.5, and 3.0 g/d, respectively, p<0.03 linear). In addition, the onset of the exercise protocol resulted in a marked drop of LDL cholesterol by ~25% in all groups. By the end of the three weeks, the HMB-supplemented groups had an additional 13% drop more than the control groups (35% decreased compared to basal, p<0.05). In conclusion, the data indicate that supplementation with Ca-HMB decreased muscle damage and breakdown resulting in a doubling of muscle accretion over the short term. In addition to the effects on muscle, HMB may have a substantial cholesterol-lowering effect.
No adverse changes in liver function tests, hematology, metabolites, psychological, or physical indices were noted, attesting to the safety of HMB.

1.2.4.3 HMB Effects/Adverse Effects

Analysis of nine human studies indicates that HMB could decrease blood total cholesterol by 5.8% ($p<0.03$) and LDL cholesterol by 7.3% ($p<0.01$) and decrease systolic blood pressure by 4.4 mm Hg ($p<0.05$).

1.2.4.4 Effect of HMB on Older Adults

A study performed at the Wichita State Human Performance Laboratory examined whether Ca-HMB supplementation could increase strength and muscle gains in older adults undergoing a two-day per week resistance training regimen. Elderly (70±1 y) men ($n=15$) and women ($n=16$) were randomly assigned in a double-blind study to either placebo or Ca-HMB (3.0 g/day) for an eight-week study period. A one repetition maximum (RM) test, body fat and lean mass (skin fold thickness) were measured prior to the study, immediately following the training program, and after four weeks and eight weeks of training. After four weeks of training, Ca-HMB increased leg strength, and after eight weeks, Ca-HMB supplementation resulted in more lean mass gain and fat loss compared with the placebo group. In conclusion, significant gains in muscular strength and lean mass could be accomplished in the older population with Ca-HMB supplementation.

1.2.4.5 Effect of a Combination of HMB, Arginine and Glutamine in Normal Humans

We have recently chosen AIDS-cachexia as a model for understanding the role of nutritional supplements in alleviating muscle wasting. In a phase I trial, we examined the safety of daily supplementation with the nutrient mixture HMB/glutamine/arginine (HMB/Gln/Arg). We studied forty normal male volunteers and assigned them to either a placebo or an HMB/Gln/Arg supplemented group (3.0 g of HMB + 14 g of Gln and 14 g of Arg given in two divided doses per day). During the four-week study, half of the subjects underwent an exercise program while the other half continued a sedentary lifestyle. Body composition (underwater weight) and strength (bench press) were measured before and at the end of the study. Blood was drawn prior to the experiment and at two and four weeks for chem screens. The data attested to the safety of HMB/Arg/Gln mixture; there were no adverse effects noted. Blood studies did not show any adverse effects recorded, and there were no changes in hematologic, liver, and kidney function noted.

1.2.4.6 A Non-pharmacological Method to Treat AIDS-associated Body Tissue Wasting

Effect of a nutritional mixture of HMB, glutamine and arginine: We examined the combination of three nutrients, HMB/Gln/Arg, in patients with AIDS-associated wasting. We postulated that these three nutrients could independently and synergistically alter the course of muscle wasting in patients with established AIDS. Sixty-eight subjects were recruited from the HIV Clinic at Nassau County Medical Center (East Hempstead, NY). They underwent randomization, in a double-blind eight-week study and were given either a placebo or HMB/Gln/Arg (3.0 grams HMB, 14 grams Gln, and 14 grams Arg). Lean body mass and fat mass were measured by an air displacement plethysmography upon enrollment and at four and eight weeks. Forty-three subjects completed the eight-week protocol. (Placebo, $n=21$, HMB/Arg/Gln, $n=22$). At eight weeks the subjects consuming HMB/Arg/Gln mixture gained 3.0±0.5 kg ($p<0.01$), which was predominantly lean body mass (2.6±0.8 kg, $p<0.005$). The placebo-supplemented group gained 0.4±0.8 kg but lost 0.7 kg of lean body mass. These data indicate that supplementation with the HMB/Arg/Gln mixture reversed the course of lean tissue loss in patients with AIDS-associated wasting.

1.2.4.7 Juven® for Cancer Cachexia

An ongoing trial at North Shore Hospital is using the same study design used in the AIDS cachexia to study the effects of the three-nutrient mixture (HMB/Gln/Arg) on patients with cancer cachexia. The preliminary intent-to-treat results (unpublished data) in 26 patients (15 active mixture, 11 placebo) shows that the treated patients have a mean muscle mass gain (fat free mass) of 1.1 kg and a mean overall weight gain of 1.7 kg. The control patients have a mean muscle mass loss (fat free mass) of −1.1 kg and a mean weight loss of only 1.4 kg.

1.3 Rationale for Current Study

Loss of lean body mass (LBM) is the earliest manifestation of the wasting syndrome seen in cancer patients. The loss in LBM occurs prior to any changes in total body weight with a relative net preservation of total body fat. We hypothesize that we may be able to override the hypercatabolic state seen in the patient with cancer by appropriate tissue-specific nutrition. The tissue-specific nutrition we have chosen consists of an adequate supply of amino acids (the necessary “building blocks”) required by rapidly
turning over cells such as intestinal mucosa and bone marrow cells. Glutamine and arginine are two such amino acids that are preferentially utilized by rapidly turning over cells (e.g. intestinal cells, colonocytes, bone marrow, etc.). The leucine metabolite, HMB, is supplied to prevent excessive muscle proteolysis, as has already been determined by in vitro studies and many studies carried out in animals and humans. L-arginine and L-glutamine are naturally-occurring amino acids found in the body and in various dietary proteins; they have been shown to improve the immune function and in some cases, prevent muscle wasting in humans. We postulate that the combination of these two amino acids with HMB will result in synergistic actions on both muscle metabolism as well as on the immune function.

Weight loss is important physically and emotionally to cancer patients. Approaches to cancer cachexia can be important even in the absence of control of the underlying disease process. Patients that are losing weight due to cancer have significantly worse quality of life than weight-stable patients. DeConno et al. indicated increased vigor in patients that achieved weight gain. There is an established link between cachexia, quality of life, and fatigue. This study will examine quality of life, using the Spitzer Quality of Life Index (SQLI), and fatigue, using the Schwartz Cancer Fatigue Scale (SCFS). This study will test the hypothesis that increasing LBM or stabilizing the loss of LBM is related to improved or stable quality of life and fatigue compared to patients with decreasing LBM.

To test the effects of treatment on patients with cancer cachexia, the changes in patient weight and muscle mass must be measured. The gold standard for measurement is body plethysmography. This expensive equipment has limited availability. Another commonly-used measurement is bioimpedance. This technique requires special equipment which is more reasonable in cost but again, has limited availability. The simplest measurements use the circumference of parts of the body and skin-fold measurements. These techniques can be done with minimal investment (a tape measure and skin-fold calipers). No study has directly compared the results of these three techniques in large scale, multi-observer studies. Therefore, one goal of this study is to determine which techniques are suitable for multi-institutional trials.

2.0 OBJECTIVES

2.1 Compare the change in lean body mass (LBM) between patients being given Juven® and patients given a non-Juven® supplement

2.2 Compare the change in fatigue and quality of life between patients being given Juven® and patients given a non-Juven® supplement

2.3 Compare the results of three body composition measurement techniques: plethysmography, bioimpedance, and skinfold measurement

2.4 Compare the change in weight between patients being given Juven® and patients given a non-Juven® supplement

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (6/11/03)

3.1.1 Patients with histologic/cytologic diagnosis of cancer, Stages III or IV at presentation or patients of any stage at presentation with current metastatic disease; measurable disease need not be present.

3.1.2 Patients with solid tumors (including lymphomas with no leukemic aspect), except brain tumors (primary or metastatic)

3.1.3 Patients who have demonstrated a weight loss of at least 2% and not more than 10% (relative to the patient’s current weight) in the previous three months

3.1.4 Patients with a Zubrod of 0-2

3.1.5 Patients must have an expected survival of three months or greater.

3.1.6 At least three weeks since major surgery; at least one week since minor surgery

3.1.7 Chemotherapy and/or radiation therapy are acceptable during treatment.

3.1.8 Enteral feedings from a PEG tube or nasogastric tube are allowed.

3.1.9 Pretreatment evaluations must be completed as specified in Section 4.0.

3.1.10 Patients must sign a study-specific consent form prior to study entry.

3.2 Ineligibility Criteria (6/11/03)

3.2.1 Patients with current intestinal obstruction are ineligible; those patients with previous obstruction are allowed.
3.2.2 Metabolic disorder, hypercalcemia, enteric fistula, or uncontrolled infections
3.2.3 Persistent moderate or severe peripheral edema, ascites, or uncontrolled congestive heart failure, or other serious medical illness
3.2.4 Patients currently taking known appetite stimulants such as megestrol acetate, dexamethasone (corticosteroid), or dronabinol (Patients on intermittent dexamethasone during chemotherapy are eligible).
3.2.5 Patients currently receiving parenteral feedings are ineligible; patients receiving enteral feedings through feeding tubes are eligible.
3.2.6 Women who are presently pregnant or nursing are ineligible, as Juven® has not been tested in pregnant or nursing women.
3.2.7 Current use of omega 3 fatty acids (such as ProSure™, Ross Laboratories) or their congeners

4.0 PRETREATMENT EVALUATIONS (6/11/03)

4.1 Required Evaluations
4.1.1 The Initial Evaluation Form (I1) must be completed and submitted at the time of randomization (See Section 5.3).
4.1.2 History and physical, including Zubrod Performance Status, weight, and evaluation of current disease state of the patient (remission, active primary, known metastatic disease). The weight and performance status must be obtained within 72 hour prior to randomization.
4.1.3 The Schwartz Cancer Fatigue Scale (SCFS) and the Spitzer Quality of Life Index (SQLI)
4.1.4 All centers must measure Lean Body Mass (LBM) by circumference and skinfold measurements, as well as by bioimpedance. BOD POD® can be used, with circumference and skinfold and bioimpedance measurements, if the appropriate equipment is available.
4.1.5 Complete blood count, platelets, AST, alkaline phosphatase, bilirubin, glucose, total protein, albumin, creatinine, BUN, pre-albumin, urinalysis within two weeks prior to registration
4.1.6 Pregnancy test for women of childbearing potential

5.0 REGISTRATION PROCEDURES

5.1 Institutions must be able to measure bioimpedance in order to participate in this protocol. Site bioimpedance equipment must be approved by the study chair, Dr. Berk, based on the criteria in Section 11.3.2.1 prior to registering the first case.

5.2 Each institution must submit a Study Agent Shipment Form (Appendix IV) to the CTSU Regulatory Office (215-569-0206) as soon as the individual responsible for the study agent has been identified. Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). This must be done prior to registration of the institution’s first case (the shipment form is only submitted once). Allow adequate processing time (7-10 days) before calling to register your first case. When the institution’s Shipment Form is received, Headquarters will forward the drug request to MTI Biotech and will send the site a videotape/training material packet (See Section 11.3.2.1). (9/2/03, 12/26/03, 3/25/04)

5.3 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail.

The Eligibility Checklist and the Initial Evaluation Form (I1) must be completed in their entireties prior to calling RTOG. Once the patient has been registered and a case number assigned, the site will write the study and case numbers on the I1 and fax the form to Headquarters, FAX # 215-574-0300. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY
Palliative radiation therapy may be given as needed, and documented on the I1 and F1 forms (See Section 12.1).
7.0 DRUG THERAPY (DOUBLE BLIND)

7.1 Treatment Plan

7.1.1 Subjects assigned to the Juven® supplement will receive a mixture containing 14 gm arginine (free-base), 14 gm glutamine, and 3 gm HMB (calcium salt) daily (Arg/Gln/HMB) in two equal doses daily, every day for eight weeks. All the amino acids will be given as the l-isomer.

7.1.2 Subjects assigned to the non-Juven® supplement will receive a mixture of l-alanine, 7.72 gm; glycine, 4.28 gm; l-serine, 2.96 gm; l-glutamic acid, 1.23 gm, gelatin, 30.52 g in two equal doses daily, every day for eight weeks.

7.1.3 Administration Guidelines
Each group will receive the supplement in a foil sealed packet; each dose will be supplied in a separate packet and will be allocated by subject number. Patients will mix the powdered supplement with eight ounces of water, drinking one supplement packet in the morning with breakfast and one in the evening with dinner; patients should be instructed to take the supplement with meals. The Juven® and the non-Juven® supplements have a mild orange taste, and it is anticipated that the taste of the supplements will not be a barrier to patient compliance.

7.1.4 Concomitant Therapy (6/11/03)
Patients should not take amino acid supplements or omega-e-fatty acids (such as ProSure™, Ross Laboratories) while on study. The use of other supplements, such as Ensure and Boost, are allowed.

7.1.5 Nutritional Data
Each of the treatments will supply 7.18 gm of amino acid nitrogen per day, 410 mg (21 mEq) of calcium, 206 mg of phosphorous, and 520 mg (27 mEq) of potassium per day. Each mixture of amino acids will be formulated into an orange flavored drink mix using the same or similar formulation of flavorings and sweeteners. The calorie content is calculated to be approximately 183 calories per day for the Juven® (Arg/Gln/HMB) treatment and approximately 200 calories per day for the non-Juven® (Ala/Gly/Ser/Glu) treatment.

7.1.6 Toxicities
Juven® is usually well tolerated with no reported side effects or known negative interactions with prescription drugs. There are no known side effects or risks associated with ingestion of any of the amino acids in the supplements; the doses to be administered fall within the acceptable levels consumed in food products.

Cancer patients have experienced more adverse GI reactions to Juven® than other populations. These reactions could be attributed to either the disease or to Juven®. Simple measures, such as diluting the packet in more than 8 ounces of water or consuming the total beverage in 4-5 sittings rather than 1-2, can be employed to alleviate these reactions.

7.1.7 Supply and Distribution (9/2/03, 12/26/03, 3/25/04)
7.1.7.1 Both of the nutritional supplements, both Juven® and non-Juven®, will be supplied and distributed by MTI BioTech, Inc. and will be supplied free of charge for this study. Each institution must submit a Study Agent Shipping Form (Appendix IV) to CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). Headquarters will forward the drug request to MTI BioTech. This must be done prior to registration of the institution’s first case.

7.1.7.2 Nutritional supplement for patients registered Monday-Thursday between 8:30 a.m. and 2:30 p.m. eastern time will be shipped via overnight carrier to arrive the following business day. Nutritional supplement for patients registered Monday-Thursday between 2:30 and 5:00 p.m. or on Fridays will be shipped the next business day.

Note: Nutritional supplement will only be shipped Monday-Thursday. There will be no weekend or holiday delivery. There also will be no supplement shipped on or between December 23 and January 1. If an institution needs nutrition supplement prior to a holiday, the institution should provide 2 days notice. If a patient withdraws consent or withdraws from the study, all nutritional supplement should be destroyed on site and documented appropriately.
7.2 Dose Modification
If the patient does not tolerate the full dose of Juven® or the non-Juven® supplement, i.e., has nausea not controllable with standard anti-emetic regimens, severe headache not responsive to standard analgesic regimens, or has other severe reactions thought to be secondary to the nutritional supplement, then one dose should be taken daily for one week and then the twice-daily dose resumed. If the patient cannot tolerate the full dose thereafter, the patient can take a single dose of the supplement per day.

7.3 Toxicity Reporting Guidelines
7.3.1 This study will utilize the Common Toxicity Criteria (CTC) Version 2.0 for grading all toxicities associated with this protocol. A copy of the CTC version can be downloaded from the CTEP home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

7.3.2 This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

7.3.3 Adverse Drug Reaction Reporting — Commercial Agent(s)
The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses a commercial anticancer agent. The following ADRs experienced by patients accrued to this protocol and attributed to the commercial agent(s) should be reported by telephone to RTOG Headquarters within 24 hours of discovery followed by a FDA Form 3500 (Medwatch) sent to the address on the form and to RTOG Data Management within 10 working days. Sites also are responsible for reporting adverse events as specified by their Institutional Review Board.

7.3.3.1 Any ADR that is both serious (life threatening [grade 4] or fatal [grade 5]) and unexpected;
7.3.3.2 Any increased incidence of a known ADR, which has been reported in the package insert or the literature;
7.3.3.3 Any ADR that results in significant disability or incapacity;
7.3.3.4 Any infant born to a patient that was treated on this protocol and has a congenital anomaly or birth defect;
7.3.3.5 Any death on study if clearly related to the commercial agent(s).
7.3.3.6 The ADR report should be documented on FDA Form 3500 (Medwatch) and mailed or faxed to the address on the form, as well as to the RTOG Data Management Department:

RTOG Data Management
1101 Market Street, 14th floor
Philadelphia, PA 19107
Phone: 1-800-227-5463, ext. 4189
Fax (215) 928-0153

All MedWatch forms submitted to RTOG Headquarters must include the RTOG study and case numbers; for studies that are not coordinated by RTOG, intergroup study and case numbers must be included.

7.3.4 Death from any cause while the patient is receiving protocol treatment or up to 30 days after the last protocol treatment, must be telephoned to the RTOG Headquarters Data Management department within 24 hours of discovery.

7.3.5 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.info.nih.gov. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification. This form will take the place of the FDA Form 3500 and must be mailed/faxed within 30 days of AML/MDS diagnosis to the Investigational Drug Branch (IDB) and to the RTOG Data Management Department:

Investigational Drug Branch (NCI/CTEP)
P.O Box 30012
Bethesda, MD 20824
Fax: 301-230-0159

AML/MDS Report
RTOG Headquarters
1101 Market Street, 14th floor
Philadelphia, PA 19107
Phone: 1-800-227-5463, ext. 4189
All AML/MDS forms submitted to RTOG Headquarters must include the RTOG study and case numbers; for studies that are not coordinated by RTOG, the intergroup study and case numbers must be included.

8.0 SURGERY
Not applicable to this study.

9.0 OTHER THERAPY
Not applicable to this study.

10.0 PATHOLOGY
Not applicable to this study

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (6/11/03)

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Pre-entry</th>
<th>4 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>History &amp; physical examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Schwartz Cancer Fatigue Scale (SCFS) and Spitzer Quality of Life Index (SQLI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Body weight</td>
<td>X^a</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LBM Measurement: circumference, and skinfold, bioimpedance, and (if available)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BOD POD®</td>
<td>X^a</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Laboratory studies^b</td>
<td>X^c</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X^c</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>X^c</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. BOD POD® can be used, with circumference and skinfold and bioimpedance measurements, if the appropriate equipment is available.

b. CBC, platelets, AST, alkaline phosphatase, bilirubin, glucose, total protein, albumin, creatinine, BUN, pre-albumin

c. Within two weeks prior to registration

def. Within 72 hours prior to randomization

e. For women of childbearing potential

11.2 Pre-Treatment
Once the individual has been selected to participate, he/she will be scheduled to meet with the responsible physician or other trained health care practitioner for full detailed explanation of the nutritional supplementation as well as obtaining informed consent for participation in the study.

11.3 Evaluation During Treatment (6/11/03)
Subjects will be studied at baseline (within 72 hours prior to initiating nutritional supplementation), and every four weeks as follows:

11.3.1 (6/11/03) At Four Weeks: The subject will be instructed to visit for measurements of body weight, vital signs, health questionnaires, urine sample, body composition testing, and to receive the supplements for the following four weeks.

11.3.2 Body Composition Testing: The required measurements are outlined in the table above and are described below:

11.3.2.1 Circumference and Skinfold: All study centers will have training in the measurement of circumferences and skinfolds via a videotape/training material packet. RTOG Headquarters will distribute the training packet to the site when the site submits a Study Agent Shipment Form (Appendix IV). A tape measure is used to record the circumference of the subject’s upper arm, forearm, waist, hips, and thigh. For skin-fold measurements a pinch of skin between two fingers is
taken on the subject’s chest, axilla, tricep, subscapular, abdominal, supra iliac, and thigh and measured using calipers to determine the thickness of the overlying fat and skin layer. The patient’s baseline measurements will serve as the control for determining body composition changes. The same person should take the initial and follow-up measurements for an individual patient, if possible.

11.3.2.2 Bioimpedance: Electrodes are placed at specific sites on the hands and foot of the individual; these are connected to the bioimpedance analyzer. A small electric current (that is not felt by the individual) goes through the electrodes and recordings are made. Measurements will be standardized according to procedures outlined by RJL System (Appendix V). Data will be submitted on the Initial Evaluation Form (I1) at pre-treatment, then on the Follow-up Form (F1) at 4 and 8 weeks (See Section 12.1). Cyprus software, which uses the standard published equations, will be used to analyze the data.

(4/8/04) Institutions must be able to measure bioimpedance in order to participate in this protocol. Sites that have bioimpedance equipment must fax detailed descriptions of the bioimpedance equipment to John A. Rathmacher, PhD, FAX # 515-296-0908, for approval prior to registering their first case. Dr. Rathmacher will contact RTOG Headquarters with his approval.

(4/8/04) Sites that do not have bioimpedance equipment available but can enter at least 15 patients on study, can contact John A. Rathmacher, PhD, 515-296-0909 at MTI BioTech. MTI BioTech will provide BIA-body composition equipment (at no cost) to these RTOG sites.

11.3.2.3 BOD POD® (if available): Changes in lean body mass and fat mass are determined by air displacement plethysmography (BOD POD®, LMI, Concord, CA). Subjects will be weighed then placed in a chamber for body volume measurements. Following this, they are connected to a breathing circuit to measure lung air volume.

(4/8/04) Sites that have BOD POD® equipment available must fax detailed descriptions of the equipment and information on measurement standards to John A. Rathmacher, PhD, Fax # 515-296-0908, for approval prior to registering their first case. Dr. Rathmacher will contact RTOG Headquarters with his approval. No BOD POD® equipment will be supplied for this study.

11.3.3 Patient Compliance: Patient compliance will be measured by counting remaining Juven® packets at the four week and eight week evaluations.

11.4 Fatigue/Quality of Life Assessments

11.4.1 Schwartz Cancer Fatigue Scale (SCFS): The SCFS is a six-item questionnaire that is patient self-administered. The SCFS is to be given to the patient prior to starting Juven®/placebo, then at 4 and 8 weeks. The questionnaire will be scored as a sum of all items with a result ranging from 6-30. The questionnaire has excellent internal consistency and reliability (alpha>0.90).

11.4.2 Spitzer Quality of Life Index (SQLI): The SQLI is a five-item categorical questionnaire summed in a Likert format with total scores ranging from 0-10. There are no subscale scores for the SQLI. The reliability and validity have been established. The SQLI has been applied as both a rater-assessed form and a patient self-assessment form. We will be using the SQLI as a patient self-assessment form.

11.5 Evaluation of Response

Following body composition testing at four weeks, patients with weight loss of 5% or greater from baseline will be considered a failure and discontinued from the study.

12.0 DATA COLLECTION (6/11/03)

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>At randomization</td>
</tr>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Schwartz Cancer Fatigue Scale (SC)</td>
<td></td>
</tr>
<tr>
<td>Spitzer Quality of Life Index (SP)</td>
<td></td>
</tr>
</tbody>
</table>
Follow-up Form (F1)  At 4 and 8 weeks (2 follow-up visits)
Schwartz Cancer Fatigue Scale (SC)
Spitzer Quality of Life Index (SP)
Treatment Summary Form (TF)

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints
13.1.1 Compare change in lean body mass (LBM) between Juven® and non-Juven®:
- Circumferences of the forearm, upper arm, thigh, waist, and hips will be taken to determine whether
  regional changes in body composition occur.
- Skinfold measurements will allow measurement of the percent body fat estimated from the Siri equation,60
  and evaluate regional changes in body fat, as outlined by Jackson and Pollock.58
- Bioelectrical bioimpedance analysis will measure changes in lean body mass, body cell mass, and fat mass
  using the equations of Kotler et al.59
- Air displacement plethysmography measurements of lean body mass and fat mass will be determined using
  the BOD POD®. Subjects will be placed in a chamber for body volume and lung air measurements will be
  done according to the manufacturer’s instructions. Calculation of lean body mass and fat mass will then be
determined using the Siri equation.60
- Body weight

13.1.2 Compare change in fatigue and quality of life (QOL) between Juven® and non-Juven®;

13.1.3 Correlate change in LBM between body plethysmography, bioimpedance, and skin-fold measurement;

13.1.4 Body weight will be followed as a secondary endpoint. The relationship of body weight to lean body
mass changes will be analyzed. It is expected that the majority of body weight changes will be secondary
to lean body mass changes.

13.2 Sample Size

13.2.1 Lean Body Mass Endpoint
The primary endpoint in this double-blind study is change in LBM from study entry to eight weeks, as
measured by bioimpedance  \( \frac{\text{LBM}_{\text{entry}} - \text{LBM}_{\text{end}}}{\text{LBM}_{\text{entry}}} * 100 \).

Assuming that the non-Juven® supplement produces no improvement or a loss in LBM, then the average
change over eight weeks is 0.00. Assuming a normal distribution, then a sample size of 86 patients per
arm will ensure 90% statistical power to find a 4% improvement in LBM in the Juven® arm at the 0.05
(two-sided) significance level. This assumes that the common standard deviation is 0.08. The
randomization will be stratified by concurrent chemotherapy (yes vs. no) and existence of metastatic
disease (yes vs. no). There is particular interest in the subgroup of patients receiving chemotherapy.
Assuming 30% of the patients receive chemotherapy, then 213 patients per arm will be required in order
to have 64 patients per arm that receive chemotherapy with 80% statistical power to detect the 4%
 improvement in LBM within the subset. Assuming 10% of the patients are ineligible or die prior to eight
weeks post therapy, then 234 total patients per arm (468 total) will be required.

13.2.2 Fatigue
The Schwartz Cancer Fatigue Scale (SCFS) will be used to measure fatigue. The minimal clinically-
important difference for the SCFS is 2.1. The primary endpoint for fatigue is eight weeks. The average
change score is expected to be zero in the non-Juven® arm and 2.1 in the Juven® arm. There is
expected to be no lack of compliance in this study. If the standard deviation is less than 6.6, then there
will be 90% statistical power to detect an average reduction in fatigue of 2.1 points. A two-sided
significance level (0.05) will be used.

13.2.3 Quality of Life
There will be one quality of life instrument used in this study: the Spitzer Quality of Life Index (SQLI).
A 0.5 point difference in SQLI scores was clinically meaningful in prior RTOG studies. Ninety patients
per arm with SQLI scores at the four and eight-week points will be required to detect a clinically
meaningful difference. This sample size estimate will preserve the statistical parameters presented in
Section 13.2.1

13.2.4 Weight
Assuming that the non-Juven® supplement produces no improvement or a loss in weight, then the
average change over eight weeks is 0.00. Assuming a normal distribution, then a sample size of 86
patients per arm will ensure 90% statistical power to find a 4% improvement in weight in the Juven®
arm at the 0.05 (two-sided) significance level. Subset analyses will be performed as indicated in Section 13.5.3.

13.3 Patient Accrual

Patient accrual is expected to be robust. Accrual is expected to be 30 patients per month and should be completed in 16 months. If the accrual is less than 5 patients per month, this study will be re-evaluated for feasibility.

13.4 Randomization Scheme

The treatment allocation will be done using a randomized permuted block within strata. There will be check on institutional balance by treatment arm. Patients will be stratified by Primary Disease Site (lung vs. others), Concurrent Chemotherapy (yes vs. no), Evidence of Metastases (yes vs. no), and Degree of Weight Loss (2-5% vs. 6-10%).

13.5 Analysis Plans

13.5.1 Interim Analyses of Accrual and Toxicity Data

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about:

i) the patient accrual rate with projected completion date for the accrual phase

ii) the distribution of patients with respect to pretreatment characteristics

iii) the frequency and severity of the toxicities by treatment arm

iv) compliance with the submission of the QOL and fatigue questionnaires.

13.5.2 Interim Analyses of Study Endpoints (1/27/04)

There will be no interim analysis of study endpoints.

13.5.3 Analysis and Reporting of Initial Treatment Results

The major analysis will be undertaken when all patients have completed eight weeks of treatment. The usual components of this analysis are:

i) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;

ii) reporting of institutional accrual;

iii) distribution of pretreatment characteristics by treatment arm;

iv) observed results with respect to the study endpoints.

1. LBM will be measured at baseline, four, and eight weeks. Change scores from baseline to eight weeks will be assessed. Assumptions of normality and equal variances between arms will be examined. If the assumptions are met, then treatment comparisons will be made using the t test. If normality does not hold, then the Wilcoxon rank-sum test will be used. Area under the curve analysis incorporating the four week measure will be performed to determine if it corroborates the eight week results. Patients that die or do not complete the eight-week assessment will be treated as missing data. There will be an assessment as to whether the missing observations are random or informative. Body weight will be measured at baseline, four and eight weeks. The relation between body weight and lean body mass will be used to determine the distribution of weight gain (i.e. lean body mass gain versus fat or water gain).

2. Fatigue will be measured using the SCFS at baseline, four, and eight weeks. Change scores from baseline measurement to eight weeks will be assessed. Treatment comparisons will be made using the t test. Area under the curve analysis incorporating the four- week measure will be performed to determine if it corroborates the eight week results. Patients that die or do not complete the eight-week assessment will be treated as missing data. There will be an assessment as to whether the missing observations are random or informative.

3. QOL will be measured using the SQLI at baseline, four, and eight weeks. Change scores from baseline measurement to eight weeks will be assessed. Treatment comparisons will be made using the t test. Area under the curve analysis incorporating the four- week measure will be performed to determine if it corroborates the eight- week results. Patients that die or do not complete the eight-week assessment will be treated as missing data. There will be an assessment as to whether the missing observations are random or informative.

4. Patients will receive multiple body composition measurements, and these will be used to determine if the different measurement methods provide the same results. Linear regression analysis will be performed using skinfold measurement as the dependent variable and bioimpedance or BOD POD® as the independent variable. Change scores of the three body
composition methods will be correlated with the body weight and QOL to determine which method is the most sensitive to changes in other outcome measures.

5. Weight change scores from baseline to four weeks will be assessed. Treatment comparisons will be made using the $t$ test. Area under the curve analysis incorporating the four-week measure will be performed to determine if it corroborates the eight-week results. Patients that die or do not complete the eight-week assessment will be treated as missing data. There will be an assessment as to whether the missing observations are random or informative.

6. Endpoint analyses and treatment comparisons within gender and race and other subsets will be performed if there are sufficient sample sizes.

### 13.6 Gender and Minority Issues

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we make the following observations. There has been no information published to date that indicates that women have distinct responses from men to Juven®. A subset analysis will be performed to determine if such an interaction exists. The projected gender and minority accruals are shown below:

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<thead>
<tr>
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<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>8</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>212</td>
<td>238</td>
<td>450</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td><strong>220</strong></td>
<td><strong>248</strong></td>
<td><strong>468</strong></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
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<td>6</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Black or African American</td>
<td>28</td>
<td>40</td>
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<tr>
<td>Native Hawaiian or other Pacific Islander</td>
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<td>0</td>
</tr>
<tr>
<td>White</td>
<td>178</td>
<td>192</td>
<td>370</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td><strong>220</strong></td>
<td><strong>248</strong></td>
<td><strong>468</strong></td>
</tr>
</tbody>
</table>
REFERENCES


APPENDIX I
RTOG 0122
SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A DOUBLE-BLIND STUDY OF NUTRITIONAL INTERVENTION FOR THE TREATMENT OF CANCER CACHEXIA USING JUVEN® NUTRITIONAL SUPPLEMENT

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know,” is available from your doctor.

You are being asked to take part in this study because you have cancer and may experience weight loss, decreasing muscle mass, and/or fatigue.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to investigate whether receiving a nutritional supplement will prevent weight loss, loss of lean tissue (muscle mass) and/or fatigue and how this affects the quality of your life. The study will compare the effects (good and bad) of two nutritional supplements. In addition, this study will compare methods of measuring changes in weight and muscle mass.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 468 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (6/11/03)

This study involves assignment to one of two treatments. You will be randomized to one of the treatments described below. Randomization means that you are put into a group by chance. A computer will assign you to one group. Neither you nor the researcher will choose the group to which you are assigned.
You will have an approximately equal chance of being assigned to one of the following treatments:

**Treatment 1**

Twice each day for eight weeks, you will mix a packet of the nutritional supplement with eight ounces of water and drink one supplement packet in the morning with breakfast and one in the evening with dinner. The supplement is a mixture of amino acids that mainly are used by your body to make proteins and has a mild orange taste.

**Treatment 2**

Twice each day for eight weeks, you will mix a packet of the nutritional supplement with eight ounces of water and drink one supplement packet in the morning with breakfast and one in the evening with dinner. The supplement is a mixture of amino acids and calcium salt that mainly are used by your body to maintain muscle mass and your immune system and has a mild orange taste.

While you are receiving either Treatment 1 or 2, you should not take amino acid supplements or omega-3-fatty acids (such as ProSure™). If you have any questions about what type of supplements you may be taking, talk with your doctor.

If you take part in this study, you will have the following tests and procedures:

- You will have a physical examination including urinalysis and measurement of your weight and your body mass before you begin treatment; The urinalysis will be repeated and your weight and body mass also will be measured at four and eight weeks into treatment.
- You will complete two questionnaires, answering questions about your level of fatigue and the quality of your life before treatment and at four and eight weeks. The questionnaires take approximately five minutes to complete.
- You will have blood tests before treatment and at eight weeks; Approximately two teaspoons of blood will be drawn each time.
- For women able to have children, you will have a pregnancy test before you begin treatment.

The nutritional supplements will be provided to you free of charge.

In this study, your body mass or composition will be measured by methods #1 and #2 described below. Your body mass also could be measured by method #3, depending on the equipment available to your doctor:
1. **Circumference and skinfold**: involves having measurements of the circumferences of your upper arm, forearm, waist, hip and thigh. In addition, skinfolds (a pinch of skin taken between two fingers) of your chest, back of the upper arm, areas below your shoulder joint and under your shoulder blade, stomach, upper hip, and thigh will be measured with a tool called a caliper.

2. **Bioimpedance**: involves a ten-minute procedure in which electrodes, similar to those used in an electrocardiogram, are placed on your arms and legs. A small electric current, which you will not feel, goes through your body, and results are recorded.

3. **BOD POD®**: involves sitting in a closed chamber with a large acrylic window for three to five minutes while measurements are taken. You will sit in the chamber (in underwear or a swimsuit and cap because clothing and hair interfere with the measurements) and be asked to relax and breathe normally for a measurement. The chamber door is opened for a minute between each measurement, which lasts 50 seconds. You will be connected to a breathing circuit, continuing to breathe normally for about two to three full breaths, and then be asked to puff three times into a disposable breathing tube while measurements are taken.

**HOW LONG WILL I BE IN THE STUDY?**

You will be in the study for eight weeks. As described above, you will have tests and procedures before treatment, at four weeks into treatment, and at eight weeks.

**WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict.

**Nutritional Supplements**

The nutritional supplements are made up of naturally occurring nutrients commonly found in food and in the body. There are no known side effects or risks associated with taking these supplements, when taken within the stated guidelines. The levels you will be taking fall within the acceptable amounts consumed in food products.
However, cancer patients may experience more stomach or bowel reactions when taking nutritional supplements than people without cancer. You may use more than 8 ounces of water to make the supplement and/or you can drink the supplement in 4 to 5 sittings, instead of only 1 or 2 during the day.

(6/11/03) Reproductive Risks: This study may be harmful to a nursing infant or an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus or to a nursing infant. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while you are on this study, you must tell your doctor immediately.

**BOD POD®**

While there are no risks involved in this measuring method, some individuals who are claustrophobic may find the closed chamber uncomfortable.

**Bioimpedance**

There are no known risks with bioimpedance. A small electric current goes through the body, but you will not feel it.

**Blood tests**

When blood is drawn, there may be some swelling, tenderness, and bruising at the site of puncture. There is also a very minor risk that the puncture may get infected.

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. You may experience some weight gain and that may in turn result in a feeling of well being. There is also the possibility that the nutritional supplement may help you tolerate chemotherapy with fewer side effects. If there is no direct benefit to you, we hope future patients may benefit from information obtained in this study.
WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) other nutritional supplements or (2) no treatment except medications to make you feel better.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

The nutritional supplements described above will be provided to you free of charge for this study.

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.
WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. If you are continuing to lose weight from your beginning weight, you can stop taking the supplement, inform the study supervisor of your decision, and return all unused nutritional supplement. Leaving the study will not affect your current medical care or result in any penalty or loss of benefits to which you are entitled. We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For information about your disease and research-related injury, you may contact:

_________________________  ________________
Name                      Telephone Number

For information about this study, you may contact:

_________________________  ________________
Name                      Telephone Number

For information about your rights as a research subject, you may contact:
(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

_________________________  ________________
Name                      Telephone Number
WHERE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615


SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

_____________________ _________________ ___________
Patient’s Name                               Signature             Date

_____________________                         __________________   ___________
Name of Person Obtaining Consent         Signature             Date
# APPENDIX II

## KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

## ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).</td>
</tr>
</tbody>
</table>
APPENDIX III

ADVERSE EVENT REPORTING GUIDELINES

Federal Regulations require that investigators report adverse events and reactions in a timely manner. This reporting improves patient care and scientific communication by providing information to the National Cancer Institute (NCI) whereby new findings can be more widely disseminated to investigators and scientists.

A. Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at initiation of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to commencement of treatment or an event, though present at the commencement of treatment, becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

**Known/expected** events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form, or noted in the drug insert.

**Unknown/unexpected** events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

**Assessment of Attribution**

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

- **Definite:** The adverse event is clearly related to the treatment/procedure.
- **Probable:** The adverse event is likely related to the treatment/procedure.
- **Possible:** The adverse event may be related to the treatment/procedure.
- **Unlikely:** The adverse event is doubtfully related to the treatment/procedure.
- **Unrelated:** The adverse event is clearly NOT related to the treatment/procedure.

B. Grading of Adverse Events

Unless specified otherwise, the NCI Common Toxicity Criteria (CTC) version 2.0 is used to grade severity of adverse events. Protocols approved prior to March 1998 will use one of several different morbidity grading systems. To grade severity of adverse events in studies prior to this date, consult the protocol document for the appropriate rating system.

C. General Guidelines

In order to assure prompt and complete reporting of adverse events and toxicity, the following general guidelines must be observed. The guidelines apply to all RTOG studies. **When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supercede the General Guidelines.** A protocol may stipulate that specific grade 4 events attributable to treatment are expected and therefore may not require the standard reporting; however, exceptions to standard reporting must be specified in the text of the protocol.

1. The Principal Investigator will report to the RTOG Group Chair, to the Headquarters Data Management Staff (215/574-3214) and to the Study Chair within 24 hours of discovery, the details of all unexpected severe, life-threatening (grade 4) and fatal (grade 5) adverse events if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.

2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require telephone notification within 24 hours of discovery.
3. A written report, including all relevant clinical information and all study forms due up to and including the date of the event, will be sent by mail or FAX (215/928-0153) to RTOG Headquarters within 10 working days of the telephone report (unless specified otherwise within the protocol). The material must be labeled: ATTENTION: Adverse Event Reporting.

   a. The Group Chair in consultation with the Study Chair will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.

   b. For events that require telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB), the Food and Drug Administration (FDA), to another co-operative group or to the study sponsor, the investigator may first call RTOG (as outlined above) unless this will unduly delay the required notification process.

   A copy of all correspondence sent to recipients of the call, e.g. NCI, IDB, another cooperative group office (non-RTOG coordinated studies) must be submitted to RTOG Headquarters. Copies must include the RTOG study and case numbers.

4. When participating in non-RTOG coordinated intergroup studies or in RTOG sponsored pharmaceutical studies, the investigator must comply with the reporting specification required in the protocol.

5. Institutions must comply with their individual Institutional Review Board policy regarding submission of documentation of adverse events. All “expedited” adverse event reports should be sent to the local Institutional Review Board (IRB).

6. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

7. When submitting reports and supporting documentation for reports to RTOG on an RTOG protocol patient, the study number and the case number must be recorded so that the case may be associated with the appropriate study file. This includes submission of copies of FDA Form 3500 (MedWatch).

8. All data collection forms through the date of the reported event and the applicable reporting form are submitted to RTOG Headquarters data management department (Attention: Adverse Event) within 10 working days of the telephone report or sooner if specified by the protocol. Documentation must include an assessment of attribution by the investigator as previously described in section A.

9. MedWatch Forms (FDA 3500) submitted on RTOG protocol patients must be signed by the Principal Investigator.

10. All neuro-toxicity (≥ grade 3) from radiosensitizer or radioprotector drugs are to be reported to RTOG Headquarters Data Management, to the Group Chair, and to the Study Chair within 10 days of discovery.

D. Adverse Event Reporting Related to Radiation Therapy

1. All fatal events resulting from protocol radiation therapy must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management department and to the radiation therapy protocol Study Chair within 24 hours of discovery.

2. All grade 4, (CTC v 2.0 and RTOG/EORTC Late Radiation Morbidity Scoring Scheme Criteria) and life-threatening events (an event, which in view of the investigator, places the patient at immediate risk of death from the reaction) and grade 4 toxicity that is related, possibly related or probably related to protocol treatment using non-standard fractionated radiation therapy, brachytherapy, radiopharmaceuticals, high LET radiation, and radiosurgery must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management and to the radiation therapy Study Chair within 24 hours of discovery. Expected grade 4 adverse events may be excluded from telephone reporting if specifically stated in the protocol.
3. All applicable data forms and if requested, a written report, must be submitted to RTOG Headquarters within 10 working days of the telephone call.

E. Adverse Event Reporting Related to Systemic Anticancer Agents

Adverse drug reactions (ADRs) are adverse events that are related to an anticancer agent and meet certain criteria: are unexpected effects of the drug or agent, or are severe (grade 3), life-threatening (grade 4), or fatal (grade 5), even if the type of event has been previously noted to have occurred with the agent.

1. Commercial Agents/Non-Investigational Agents

<table>
<thead>
<tr>
<th>Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite</th>
<th>Increased Incidence of an Expected AE</th>
<th>Hospitalization During Treatment</th>
<th>Secondary AML/MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Form 3500&lt;sup&gt;4,5&lt;/sup&gt; within 10 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NCI/CTEP Secondary AML/MDS Form within 30 days of diagnosis&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Call RTOG within 24 hrs of event&lt;sup&gt;7&lt;/sup&gt;</td>
<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Any increased incidence of a known AE.
2. Inpatient hospitalizations or prolongation of existing hospitalization for medical events equivalent to CTC Grade 3-5 which precipitated hospitalization must be reported regardless of the requirements or phase of study, expected or unexpected and attribution.
3. Reporting required during or subsequent to protocol treatment.
4. Submitted to Investigational Drug Branch, PO Box 30012, Bethesda, MD 20924-0012.
6. All grade 5 known toxicity.
7. Call RTOG Data Management (215) 574-3214. To leave a voice mail message when the office is closed, announce that you’re reporting an “adverse event”, provide your name, institution number, and a telephone number where you may be contacted.

2. Investigational Agents

A investigational agent is one sponsored under an Investigational New Drug Application (IND). Reporting requirements and timing are dependent on the phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator’s Brochure. An expedited adverse event report requires submission to CTEP via AdEERS (Adverse Event Expedited Report). See the CTEP Home Page, http://ctep.info.nih.gov for complete details and copies of the report forms.

a. AdEERS (Adverse Event Expedited Reporting System)

Effective January 1, 2001, the NCI Adverse Event Expedited Reporting System (AdEERS) was implemented for all protocols for which NCI is the supplier of an investigational agent.

Attribution: An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any phase of trial. An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any phase of trial. An expedited report is not required for unexpected or expected Grade 1 adverse events for any phase of the trial.

RTOG uses “decentralized” notification. This means that all reportable events will be directly reported to NCI, just as has been done with paper-based reporting. AdEERS is an electronic reporting system; therefore, all events that
meet the criteria must be reported through the AdEERS web application. Once the report is filed with AdEERS, the institution need not send notification to RTOG, as the AdEERS system will notify the Group Office. Institutions that utilize this application are able to print the report for local distribution, i.e., IRB, etc.

For institutions without Internet access, if RTOG is the coordinating group for the study, contact RTOG Data Management (215-574-3214) to arrange for AdEERS reporting. In these instances, the appropriate Adverse Event Expedited Report template (Single or Multiple Agents) must be completed. The template must be fully completed and in compliance with the instruction manual; i.e., all mandatory sections must be completed including coding of relevant list of value (LOV) fields before sending to RTOG. Incomplete or improperly completed templates will be returned to the investigator. This will delay submission and will reflect on the timeliness of the investigators’ reporting. A copy of the form sent to RTOG must be kept at the site if local distribution is required. Do not send the template without first calling the number noted above.

Templates for Single or Multiple Agents may be printed from the CTEP web page or will be supplied from the RTOG Registrar upon faxed request (FAX) (215) 574-0300.

When reporting an event on a patient in an RTOG-coordinated study, you must record the RTOG case number in the Patient ID field.

AdEERS reporting does not replace or obviate any of the required telephone reporting procedures.

Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on separate arms: An expedited adverse event report should be submitted for an investigational agent(s) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s).

Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s): When an investigational agent(s) supplied under an NCI-sponsored IND is used in combination with a commercial agent(s), the combination should be considered investigational and reporting should follow the guidelines for investigational agents.

a. Expedited Reporting for Phase 1 Studies

<table>
<thead>
<tr>
<th>Unexpected Event</th>
<th>Expected Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grades 2-3</strong> Attribution: Possible, Probable or Definite</td>
<td><strong>Grades 4 &amp; 5 Regardless of Attribution</strong></td>
</tr>
<tr>
<td>Grade 2: Expedited report within 10 working days.</td>
<td>Report by phone to IDB(^1,2) within 24 hrs. Expedited report to follow within 10 working days.</td>
</tr>
<tr>
<td>Grade 3: Report by phone to IDB(^1,2) within 24 hrs. Expedited report to follow within 10 working days.</td>
<td>This includes deaths within 30 days of last dose of treatment with an investigational agent.</td>
</tr>
<tr>
<td>Grade 1: Adverse Event Expedited Reporting NOT required.</td>
<td>Adverse Event Expedited Reporting NOT required.</td>
</tr>
<tr>
<td><strong>Grades 4 &amp; 5 Regardless of Attribution</strong></td>
<td><strong>Grades 1 - 3</strong></td>
</tr>
<tr>
<td>Report by phone to IDB(^1,2) within 24 hrs. Expedited report to follow within 10 working days.</td>
<td>Adverse Event Expedited Reporting NOT required.</td>
</tr>
<tr>
<td>Expended report to follow within 10 working days.</td>
<td>Report by phone to IDB(^1,2) within 24 hrs.</td>
</tr>
<tr>
<td>This includes deaths within 30 days of last dose of treatment with an investigational agent.</td>
<td>Expended report to follow within 10 working days.</td>
</tr>
<tr>
<td><strong>Grades 4 &amp; 5 Regardless of Attribution</strong></td>
<td><strong>Grades 1 - 3</strong></td>
</tr>
<tr>
<td>Adverse Event Expedited Reporting NOT required.</td>
<td>Report by phone to IDB(^1,2) within 24 hrs.</td>
</tr>
<tr>
<td>Expended report to follow within 10 working days.</td>
<td>Expended report to follow within 10 working days.</td>
</tr>
<tr>
<td>This includes deaths within 30 days of the last dose of treatment with an investigational agent.</td>
<td>This includes deaths within 30 days of the last dose of treatment with an investigational agent.</td>
</tr>
</tbody>
</table>

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you’re reporting an “adverse event”, provide your name, institution number and a telephone number where you may be contacted.
2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).
c. Expedited Reporting for Phase 2 and Phase 3 Studies

<table>
<thead>
<tr>
<th>Unexpected Event</th>
<th>Expected Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grades 2-3</strong>&lt;br&gt;Attribution: Possible, Probable or Definite</td>
<td>Grades 4 &amp; 5 Regardless of Attribution</td>
</tr>
<tr>
<td>Expedited report within 10 working days.</td>
<td>Report by phone to IDB(^{1,2}) within 24 hrs. Expedited report to follow within 10 working days.</td>
</tr>
</tbody>
</table>

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an “adverse event”, provide your name, institution number and a telephone number where you may be contacted.

2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).
APPENDIX IV (9/2/03, 12/26/03, 3/25/04)

RTOG 0122

STUDY AGENT (JUVEN®) SHIPMENT FORM

Each institution must submit this form to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified and prior to registration of the institution’s first case. Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). Headquarters will forward the completed form to MTI Biotech. Allow adequate processing time (7-10 days) before calling to register the first case.

SHIP TO:

Name: ________________________________

Address: ____________________________________________  
(no P.O. addresses)
______________________________________________
______________________________________________

Telephone: ________________________________________

Fax#: ____________________________________________

RTOG Institution#: ________________________________

Institution Name: ________________________________

IRB Approval Date: ________________________________

Investigator (PI) Signature __________________________ Date: __________

Investigator Name (Print) ______________________________

Investigator NCI # ________________________________

Send Completed Form to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX 215-569-0206

RTOG Headquarters Approval __________________________ Date: __________

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APPENDIX V

Bioimpedance Testing Procedure

- The exam area should be comfortable and free of drafts and portable electric heaters.
- The exam table surface must be non-conductive and large enough for the subject to lie supine with the arms 30 degrees from the body and legs not in contact with each other.
- The BIA - 101Q analyzer battery should have a new 9 volt battery.
- The BIA - 101A analyzer and Spectrum battery should be fully charged.
- The analyzer calibration and patient cables should be checked regularly (see manual).

Subject Preparation

- The subject should not have exercised or taken a sauna within 8 hours of the study.
- The subject should refrain from alcohol intake for 12 hours prior to the study.
- The subject's height and weight should be accurately measured and recorded.
- The subject should lie quietly during the entire test.
- The subject should not be wet from sweat or urine.
- The subject should not have a fever or be in shock.
- The study and testing procedure should be explained to the subject.
APPENDIX V (continued)

Testing Procedure

• The subject should remove the right shoe and sock (generally the study is completed on the right side of the body). The body side (left or right) should always be used subsequently.
• The subject should lie supine with the arms 30 degrees from the body and legs not touching and remove jewelry on the electrode side.
• The electrode sites may be cleaned with alcohol, particularly if the skin is dry or covered with lotion.
• Attach the electrodes and patient cables as shown in the illustration.
• Turn the analyzer on and make sure the subject refrains from moving. When the measurements have stabilized, record the displayed Resistance (R) and Reactance (Xc) with the subject's name, age, gender, height and weight.
• Remove and dispose of the electrodes, be careful not injure the subject's skin or contaminate the operator.
• The entire testing time is less than 5 minutes - the BIA analyzer is on for less than one minute.
• The results are available immediately from the software program.
• The study may be repeated as often, as necessary.

Operator/examiners must demonstrate the following level of proficiency:
• Two consecutive measurements made on a single, stable subject must result in values within one percent.

There have never been any reports of morbidity or mortality associated with the study.

If you have any questions, please call RJL Systems at 1-800-528-4513 or access the RJL website at http://www.rjlsystems.com/research/electrodes.htm