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PROTOCOL 2009-0854
THE EFFECTS OF GINSENG ON CANCER-RELATED FATIGUE

A. Specific Aims

Previous research has shown that patients with cancer develop severe physical and psychosocial symptoms [1-4]. The frequency of cancer-related fatigue (CRF) varies from 60% to 90%. Despite CRF's prevalence, severity, and effects on the quality of life of patients with cancer, there are limited treatment options available [5-12]. Prior studies have revealed that CRF has a multifactorial etiology in these patients. Different mechanisms, directly or indirectly, impact brain function to cause the subjective symptom of fatigue [14, 15]. Several factors are significantly associated with CRF, including: anxiety [16], depression [16], pain [17], anorexia/cachexia [18], drowsiness [19] sleep disturbances [20], cognitive functioning [21], and performance status [13]. In recent years, several cytokines and other pro-inflammatory mediators, produced by the host in response to the presence of cancer, have been found to be associated with symptoms such as fatigue [22], pain [14,15], cognitive impairment [21], depression, cachexia, and sleep disorders [10]. Ginseng root (*Panax ginseng* C. A. Meyer, Araliaceae) has a long history of use, particularly in China, in the treatment of fatigue and debility and declining work capacity and concentration; it is also administered during convalescence [25,26]. Currently, ginseng is widely used in the United States as a traditional medicine to lessen the sense of fatigue that cancer patients experience. It has been found to have direct action on the central nervous system, including cognition/memory, sleep disturbance, anxiety/depression, pain, and the ability to modulate inflammatory cytokines [27,28]. The **rationale** for the proposed study is that, on the basis of previously described mechanisms and the results of pilot studies, *P. ginseng* seems to have a beneficial effect on fatigue, primarily in the general population and in patients with cancer [28, 29] however, *ginseng*'s duration of action, safety, tolerability, and possible mechanisms in reduction of CRF, have not been characterized. In addition, not all assessment tools used in previous studies were validated, and there was no attempt to understand the pathophysiologic characterstics of *ginseng* using laboratory correlates. The effects of *P. ginseng* on CRF and cytokine levels must be defined through randomized controlled studies using validated tools and laboratory correlates. This exploratory study will allow us to collect and store blood for future investigational studies on cytokine levels in patients with cancer who are experiencing fatigue.
Innovation Through the conduct of this study, we set forth to explore the effect of *P. ginseng* on fatigue in cancer in controlled setting using validated assessment tools and clinical objective measures. We also plan to assess its safety and tolerability. The rationale for use for the *P. ginseng* is: 1) it is the most studied ginseng in regards to safety and efficacy (both animal and human studies); 2) it is considered a stimulant as compared with another commonly used ginseng, *Panax quinquefollius*; and 3) a commercially available standardized extract will be used and therefore, it will be easily available, low cost to patients with CRF if it is found to be effective.

Our **long-term goal** is to reduce cancer related fatigue and thereby improving quality of life in patients with cancer. The **objective** of the proposed study is to explore the effects of *P. ginseng* on CRF and safety in patients with cancer. We **hypothesize** that *P. ginseng,* by its direct action on the brain is capable of reducing cancer related fatigue in patients with cancer.

We plan to test our hypothesis and accomplish the objectives of this application by performing the following ***specific aims:***

A.1. To explore effects of 800mg of *P. ginseng* as compared to placebo on cancer-related fatigue as determined by FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue) at the end of 4 weeks.

A.2. Exploratory Objectives

- To explore its effect on physical activity as measured by Six minute walk test.
- To explore its impact on quality of life-related variables, mood (HADS -- Hospital Anxiety and Depression Inventory), quality of life domains ((FACT-G)), neurocognitive motor function (SDMT) and Global Symptom Evaluation (GSE) in these patients.
- To explore its side effects and tolerability of *P. ginseng* in these patients.

We will collect and store blood/plasma samples from consenting patients (optional procedures) for future studies to explore ginseng's effect on induced monocyte inflammatory cytokines (IL-1β, IL-6, IL-10 and

TNF-α) production and the serum levels of these cytokines (IL-1β, IL-6, IL-10 and TNF-α) in cancer patients.

· To estimate the proportion of patients experiencing clinical benefit in each arm and to compare these proportions between arms

B. BACKGROUND AND SIGNIFICANCE

B.1. Theoretical Construct : The model guiding the research is an adaptation of the middle range theory of unpleasant symptoms (Figure 1) [30]. This theory describes the effects and interactions among different physiologic and psychological influences on CRF, including cognitive/memory impairment, sleep disturbances, cancer pain, cancer anorexia/cachexia, anxiety, depression, and poor quality of life. These symptoms are, in turn, influenced by tumor burden and function through tumor byproducts and immune mechanisms, such as cytokines (IL-1β, IL-6, IL-10 and TNF-α. In addition, situational factors may act as covariates in cancer and its symptoms and will be included in all analyses. We propose that P. ginseng reduces fatigue in cancer patients by its direct action on the brain and improving symptoms contributing to fatigue such as pain, anorexia, anxiety, depression (mood disturbances), and modulation of cytokines (IL-1β, IL-6, IL-10 and TNF-α) response.

B. 2.1. Inflammatory Cytokines and Fatigue

Fatigue in patients with cancer can be attributed to changes in cytokine concentrations caused by the disease or its treatment [14,23] Cytokines have been implicated in the pathophysiology of fatigue by acting at multiple levels, including mood, muscle mass, strength, and metabolic status [14,15,32-34]. In patients with metastatic colorectal cancer, high pretreatment concentrations of proinflammatory cytokines (IL-1β, IL-6, and TNF-α) are associated with fatigue, appetite loss, and poor performance status [35]. Fatigued breast cancer survivors were distinguishable from non-fatigued survivors by statistically significant increases in ex-vivo monocyte production of interleukin 6 and TNFα after lipopolysaccharide stimulation, high plasma concentrations of interleukin-1 receptor α and soluble interleukin-6 receptor (CD126), decreased monocyte cell-surface interleukin-6 receptor, and decreased frequencies of activated T lymphocytes[35]. In these patients, there was an inverse correlation between soluble and cell-surface interleukin-6 receptors, consistent with inflammation-mediated shedding of receptors, and in-vitro studies confirmed that proinflammatory cytokines induced such shedding. Other studies provide preliminary evidence of the important role of cytokines in fatigue severity (35). As IL-10 plays a important role in homeostasis in cancer patients with elevated cytokines (IL-1β, IL-6, and TNF-α), treatment with an agent which modulates the effect of IL-1β, IL-6, and TNF-α may be due changes in IL-10 [36].

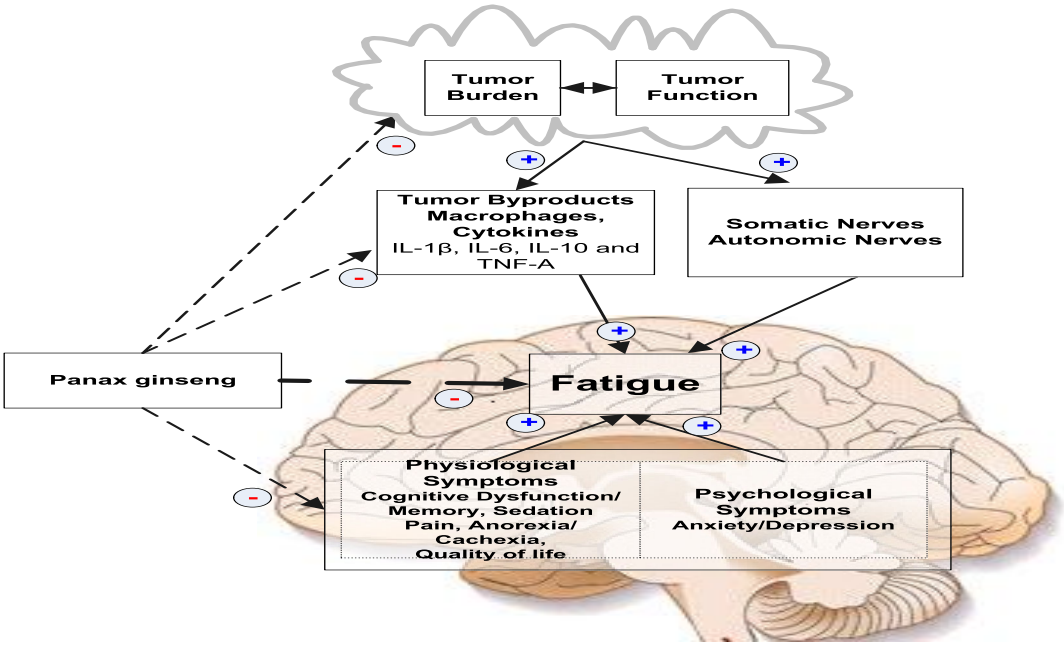


Figure 1. A diagram of an adapted middle range theory of unpleasant symptoms demonstrating the interactions between cancer and the other physiological and psychological factors that contribute to fatigue, including the impact ginseng have on each of these stages to decrease fatigue.

B. 2.2. Physiological and Psychological Factors and Fatigue

Pain, sedation, and fatigue: Undertreated or overtreated pain may contribute to fatigue. In prior studies, grade "A" evidence (highly consistent findings from multiple studies) indicated an association between pain and fatigue, and suggested that at least in some patient populations, persistent pain can be considered a causative factor [17]. Prospective studies of patients with cancer on opioids often reveal evidence of neurotoxicity. Opioid-induced neurotoxicity (OIN) may manifest as drowsiness, myoclonus, and cognitive dysfunctions, such as delirium[19, 42]. **Psychological symptoms including anxiety, depression, and fatigue**: Prior studies in cancer patients have found a significant association between fatigue intensity and psychologic` symptoms such as anxiety and depression [16].

B.2.3 Current Treatments for Cancer-Related Fatigue: Currently, research on the treatment of CRF has been limited to prospective cohort studies and a limited number of randomized controlled studies and meta-analyses [43]. In randomized controlled comparisons to placebo, corticosteroids have been found to temporarily reduce fatigue in terminally ill cancer patients, but the most appropriate type and dose of corticosteroids have not been defined [43]. These drugs appear to have significant but transient effects (usually less than 3-4 weeks) and are associated with adrenal suppression and major potential side effects, including infections, coagulopathy, myopathy, osteoporosis, and Cushing's syndrome. The stimulant, methylphenidate has been found to be effective in the treatment of fatigue in randomized controlled trials in patients with multiple sclerosis and, in preliminary reports, in patients with cancer. However, a recent randomized controlled trial in patients with cancer by our group found that methylphenidate was not superior to placebo[43]. The results of a recent study on the role of a chemically similar ginseng, Panax quinquefolius (American ginseng), in the treatment of fatigue in cancer were encouraging, but inconclusive [29]. The efficacy, dose, and side effect profile need to be further defined in these settings by using validated tools that characterize fatigue in this population, and by using sound methods.

B.3 Drug Information

B.3.1 *Panax ginseng* *Panax ginseng* C. A. Meyer (Araliaceae), also known as Asian or Korean ginseng, has been used medicinally in the Far East for several millennia and is currently one of the most widely used botanical dietary supplements in the U.S. [45]. Standardized extracts and other commercial products are prepared from dried root, which are prepared by either drying or bleaching with sulfur dioxide, or by steaming and then air drying, creating the white and red types, respectively. In addition to

P. ginseng, other plant species also go by the common name “ginseng”, in particular, other *Panax* species such as American ginseng, *Panax quinquefolius* L., and Siberian ginseng, *Eleutherococcus senticosus* (Rupr. & Maxim). For the purpose of this discussion, we will use the word ginseng to refer to *P. ginseng* unless otherwise specified. Ginseng preparations are derived from the plant root and processed into powder and used in tablets, capsules, teas, or concentrated into extracts and used in liquid or capsule form. More than 30 different ginsenosides have been identified as components of ginseng [24]. Most ginsenosides are classified as either protopanaxatriols (e.g. Rg_1, Rg_2, Re, Rf) or protopanaxadiols (e.g. Rb_1, Rb_2, Rc, Rd). The composition of ginsenosides (and protopanaxatriol/protopanaxadiol ratios) varies according to species, age of the plant, growing conditions, cultivation, part of the plant used, and preparation methods. An evaluation of multiple standardized *P. ginseng* preparations revealed that, while most preparations labeled "standardized" contained reasonably consistent amounts of labeled total ginsenosides, Rb_1/Rg_1 ratios demonstrated greater variation. This variability may contribute to some of the heterogeneity of reported findings in ginseng research, as there is some evidence that different ginsenosides have different pharmacologic effects [25]. Also, this is considered one of the major differences between *P. ginseng* and *P. quinquefolium* (American ginseng), where the ratio of Rg_1 to Rb_1 is higher in *P. ginseng*. Therefore, we will determine the ratio of Rg_1 to Rb_1 for each new sample lot and also for materials kept in storage for greater than one year to check for stability (see Appendix A for preliminary data). Ginseng has a long history of use, particularly in China, for the treatment of patients who have been debilitated by prolonged illness, especially when the illness has come from poor habits: eating irregularly, working too hard without enough rest, and anxiously worrying, and it has also been found to be useful in sick patients after all other drugs have failed. These traditional uses of ginseng often used considerably larger doses than currently recommended [47]. According to the World Health Organization and the German Commission E, ginseng root is used as a tonic for invigoration and fortification in times of fatigue and debility, for declining capacity for work and concentration, and also during convalescence [24,25]. It has also been used for the treatment of diabetes, erectile dysfunction, and gastritis. Currently, ginseng is widely used in the United States with the belief that it will improve overall energy and vitality, particularly during times of fatigue or stress. It is believed that ginseng reduces fatigue by action on: a) CNS, including cognition/memory, sleep disturbance, anxiety/ depression, b) pain, and c) inflammatory cytokines.

B.3.2 CNS Actions In vitro, in vivo studies, and clinical studies, have revealed that *ginseng* improves central nervous system function by improving cognitive function (abstract thinking ability, memory, attention, concentration, ability to complete detail-oriented editing task and ability to cope) and mood [46-48]. The exact mechanism of action is unclear, but some studies have indicated that ginseng acts on the central nervous system in one of the following ways: A) Neuroprotection [27] (either in vivo or in vitro) via potentiation of nerve growth factor activity [27,49,50], inhibition of NO production, leading to decreased oxidative stress because of reduced free radicals production [51-53], inhibition of the activity of *N*-methyl-D-aspartate(NMDA) receptor activity [54,55], inhibition of excitatotoxicity and calcium overflux into neurons, e) maintenance of cellular ATP levels, preservation of neuron structural integrity, prevention of astrocytic swelling by gensenosides, which is induced by glutamate [56], and inhibition of microglial burst activity and NO production by activated microglia [57]. B) Modulation of neurotransmission: ginsenosides modulate acetylcholine release and reuptake and the number of choline uptake sites, especially in the hippocampus [58, 59]. Ginseng has also been shown to increase dopamine and norepinephrine in the cerebral cortex [60] and modulate the activity of presynaptic and postsynaptic receptors. These actions may explain ginseng effects on attention, cognitive processing, integrated sensory-motor function, and auditory reaction time in healthy subjects [61]. Ginseng also has been found to increase serotonin levels in the cortex [62]. C) Improvement of cognition, through direct effect on the hippocampus [63] and memory [64]. D) Inhibition of inflammatory cytokines.

B.3.3 Ginseng and Pain: Opioids such as morphine are often used to treat cancer pain in patients with metastatic cancer. *P. ginseng* has been shown to exert protective effects against **morphine-induced depression of B-cell and T-cell functions** (65). Ginsenoside Rf potentiated opioid-induced analgesia in mice and inhibited tolerance to this analgesia in a dose-dependent manner (66). One possible mechanism of this activity involves the **inhibition of NMDA receptors** (67). NMDA has an important role

in the sensitization, tolerance, and occurrence of opioid-induced dysfunction. The use of ginseng may lead to reduced morphine dosages and a subsequent increase in social functioning. However, the evidence is currently limited to animal studies.

B.3.4 Ginseng and cytokines: In a 2003 study by Smolinski et al. [68] demonstrated the anti-inflammatory properties of ginsenoside Rb_1 in RAW 264.7 cells was demonstrated. These cells were chosen because of their production of high concentrations of IL-6 and TNF-α in culture, after activation by LPS. Cytokines were also evaluated in mice using LPS as a stimulant. LPS stimulated cells treated with ginsenoside Rb_1 showed a decrease in inflammatory cytokines TNF-α and IL-6 levels. This study is important as macrophages (RAW 264.7-mouse macrophage model) in humans are the primary cells felt to play a key role in the production of inflammatory cytokines and production of fatigue and also they may do so by their ability to cross the blood brain barrier. These finding were similar to those of Cho et al. [69], who found a decrease in TNF-α but no significant decrease in the IL-6. Yu and Li (2000) found that TNF-α and IL-6 mRNA expression in hippocampus of LPS stimulated rats was lower in rats who were injected with ginsenoside saponins, than in those not injected with these saponins [70]. Ginseng has ubiquitous effects on key players of the inflammation-to-cancer sequence, including inhibitory effects on inflammatory cytokines, toll-like receptors, cyclooxygenases, and kinases, which play an important role in symptoms (fatigue) and carcinogenesis [71]. To determine the effects of orally administered *P. ginseng* G115 extract on inflammatory cytokines and toll-like receptor 4 (TLR4), their expression was examined in mice that swam 1 hour a day for 4 weeks. In the stress-plus-treatment group, TLR4 levels increased gradually at the second week ($p<0.001$ vs. controls), with a peak at the third week ($p<0.001$). G115-treated stressed mice had increased TLR4 expression, and cytokines were released in a different pattern [72]. Further clinical trials are needed to delineate the role of *P. ginseng* on inflammatory cytokines and CRF.

B.3.5 Preliminary Reports on Fatigue in Clinical Trials in Cancer and Noncancer Patients

Several studies evaluating exercise performance, cognitive performance, or mental performance have found positive benefits for fatigue using Asian and American ginseng supplements. A few studies have evaluated fatigue as a primary outcome, and the results of these clinical trials have been positive, supporting the evidence found in other studies. In 2007, Barton et al. [29] reported an improvement in cancer-related fatigue after treatment with *P. quinquefolius* compared with placebo in a randomized controlled study of 282 patients with cancer. The patients were assigned to one of four groups: placebo, 750 mg of ginseng, 1000 mg of *ginseng*, and 2000 mg of ginseng per day for 8 weeks. Endpoints were measured at baseline, 4 weeks, and 8 weeks. The area under the curve (AUC) and change at week 8 from baseline were calculated. The overall completion rate was 63% (175/282). The mean AUC for fatigue, as measured by BFI (activity interference), was 551 in the 2000-mg group and 480, 467, and 460 in the 1000-mg, 750-mg, and placebo groups, respectively. The AUC for usual fatigue, as measured by BFI, was 491 in the 2000-mg group and 448, 425, and 410 in the 1000-mg, 750-mg, and placebo groups, respectively. Among placebo patients, there was a 7.3% mean change in the vitality subscale score of the SF-36 and a 5.6% improvement in well-being. With the 750-mg ginseng dose, the benefit was similar to placebo (5.3), but there was a 14.6% improvement in vitality and a 12% improvement in well-being with the 1000-mg dose. At 2000 mg, ginseng was associated with a mean improvement of 10.5% in vitality and 5% improvement in well-being. There was no statistically significant difference in adverse events among the ginseng and placebo groups. They concluded that American ginseng has some activity on fatigue at doses of 1000 mg/day and 2000 mg/day and has a tolerable toxicity profile.

Le Gal et al. (71) reported an improvement in fatigue symptoms in patients treated with *P. ginseng*, vitamins, and minerals. Two-hundred thirty-two patients, aged 25-60 years, who had had functional fatigue, received either two capsules of Pharmaton (40 mg ginseng G115, nine vitamins, and eight minerals) per day or placebo. Symptom severity was quantified by an ad hoc fatigue score. At the end of the study (day 42), the mean symptom score in the placebo group was 3.7 compared with 2.8 in the active treatment group ($p=0.019$). Seventy-one percent of patients in the Pharmaton group reported excellent efficacy compared to 50% in the placebo group. The findings of this study suggest that ginseng and vitamins are effective in treating symptoms of fatigue. However, the use of an ad hoc instrument to assess fatigue and the lack of a description of randomization and blinding procedures somewhat limit the

value of this study. A double-blind, placebo-controlled single-center pilot study was performed to evaluate the effect of *P. ginseng* on fatigue and quality of life in adult chemo-naïve cancer patients [74]. Twenty patients were evaluable (11 in the ginseng arm and nine in the placebo arm). The total fatigue level and mean value of fatigue(as measured by BFI) in the previous 24 hours were significantly improved (p=0.036 and 0.035, respectively) in the ginseng arm compared with the placebo arm. Similarly, quality of life and overall health were also improved with the use of ginseng (p=0.044 and 0.029, respectively). However, the small sample size and lack of published data warrant further studies on this drug in regards to cancer related fatigue.

B.3.6. Fatigue Related Outcomes: *Cognition: Memory and Mood:* In a 2-month, double-blind, placebo-controlled study of 112 healthy, middle-aged adults given either ginseng or placebo, results showed that ginseng improved abstract thinking ability [75]. A double blind, placebo-controlled study of 50 men found that 8-weeks of treatment with a ginseng extract improved the men's ability to complete a detail-oriented editing task [74]. A double-blind trial of 16 healthy males found favorable changes in the subjects' ability to perform mental arithmetic in those given ginseng for 12 weeks [61]. In addition, comprehensive benefits were seen in a double-blind, placebo-controlled trial of 60 seniors given ginseng for 50 or 100 days [77]. *P. ginseng* improved in numerous measures of mental function, including memory, attention, concentration, and ability to cope [71]. However, four double-blind, placebo-controlled studies evaluated the combination of ginseng and ginkgo and found inconsistent evidence of improved mental function [79-82]. In 2007, Wei et al. [82] reported the anxiolytic effects of ginseng in mice. This study found improvement in several anxiety paradigms, including the elevated plus-maze test, light/dark test, hole-board test and isolation-induced aggression test. Other animal studies also observed similar results [84, 85]. Tode et al. [85] observed that anxiety levels as measured by State-trait Anxiety inventory scores, in menopausal women declined to normal after 30 days of ginseng treatment. Hence, further studies are needed to elucidate the role of *P. ginseng* in anxiety and depression. *Exercise Performance: P. ginseng* has found to be beneficial as a mild ergogenic aid, but published evidence remains incomplete and contradictory [76, 77, 87, and 88]. Other forms of ginseng generally lack any evidence of benefit. *General Well-Being:* Several studies have shown equivocal or no evidence of improvement in well being [79-90].

B.4.1. Ginseng Product Justification

We will be acquiring the ginseng product and placebo pill from Indena (Milan, Italy), a company specializing in the production of high quality botanical dietary supplements. The placebo will be identical to the drug, but will contain methylcellulose as the inert ingredient, and will not require any methods to mask odor. The rationale for using this product is three-fold, a) ginseng is a widely available and relatively inexpensive, b) it is the most widely studied standardized extract and provides a consistent level of ginsenosides, c) the producer of this product, Indena, is well-respected and is known to apply good agricultural and manufacturing practices. The proposed research project will comply with "NCCAM Interim Policy: Biologically Active Agents Used in Complementary and Alternative Medicine (CAM) and Placebo Materials" [91].

- **B.4.2. Ginseng Dosage Justification:** There are no published randomized controlled trials on P.ginseng for the management of Cancer related fatigue with the dose of 800mg/day.
- In literature there are clinical trials which have used upto 9 grams of root (100mg of ginseng extract is equivalent to approximately 500mg of dried ginseng radix)[ref: Heo et al 08, and Lee et al 08].
- These studies were done in elderly Alzheimers patients with not significant difference in the safety profile in the treatment arm and placebo, other references are Kennedy et al 2001 and Oh etal 2010(125-127)
- However due to limited literature in cancer patients (Barton et al Journal of supportive care 2009: American ginseng) and unclear methodology to compare the product used in the published literature as compared to this study, we would plan a two phase study for more rigorous safety monitoring. This now added to the revised protocol, informed consent document, and safety monitoring documents.

- We plan to do a 2 phase study, an initial non dose escalating phase of 30 patients to evaluate dose limiting toxicity and a second phase- RCT double blind phase with 64 patients in each arm.

Heo et al 2008(125):
An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer_s disease(Dosage 0(control), 4.5g and 9 g). The study uses the same root as the proposed study however we use an extract.
No significant difference in adverse events was found between the three treatment oups (P = 0.912). Two patients in the low-dose KRS group complained of feeling feverish and two patients in the high-dose KRS group complained of nausea. Three participants in the control group reported symptoms of nausea, diarrhoea and headache respectively. All the subjects who reported adverse effects withdrew from the study.

Oh et al. 2010(127):
Thirty-two menopausal women participated in a placebo-controlled, double-blind, crossover clinical study with administration of either three capsules of Korean red ginseng extract (1 g per capsule) or placebo daily. There were no severe adverse events in the ginseng group, although two cases of vaginal bleeding occurred during ginseng treatment

Ginseng Product: Panax ginseng: The drug used for this clinical trial is an Standardized Panax ginseng root extract (supplied by Indena, S.P.A., Milan Italy compliant with NCCAM product quality [91] (See APPENDIX K for drug and placebo information and letter of support from Indena), has been standardized for total ginsenosides and ginsenoside ratio of the major ginsenosides. The matching placebo will use colored capsules for similar appearance since ginseng extract has little or no odor that needs blinding, and it will include the inactive excipient methylcellulose.

There are no published randomized controlled trials on P.ginseng for the management of Cancer related fatigue with the dose of 800mg/day. The currently recommended dosage of P. ginseng is 2 to 3 g per day of dried plant material, or 300 to 900 mg/day of a standardized extract, containing 4% to 7% ginsenosides [24-26, 44, 45,125-127– WHO monographs and German Commission E]. However, the Pharmacopoeia of the People's Republic of China lists recommended dosages of 3 to 9 g of the root as a tea, with higher dosages recommended for more debilitated patients [46]. A number of clinical trials (Table 1) have been performed using a variety of doses ranging from 40 to 800 mg of ginseng extract and 2 to 6 g of plant material. In this study, we will use a dosage of 800 mg per day to explore ginseng's effect on cancer related fatigue. This dosage is based on currently recommended dosages and historical use. Furthermore, these dosages have been confirmed as reasonable, in regards to efficacy and safety, upon consultation by Mark Blumenthal (founder and executive director of the American Botanical Council (ABC), and the editor/publisher of Herbal Gram), and Dr. Lorenzo Cohen (Professor) and Dr. Moshe Frenkel (Medical Director), both with Integrative Medicine Program, M.D. Anderson Cancer Center).

Table 1. Dosages of *Panax ginseng* previously used in clinical trials

Author	Number of Patients	Treatment Duration (Days)	Daily Dose (g)
Andrade, et al., 2007 [92]	60	144	3
Hong B, 2002 [93]	45	96	2.7
Ellis J, Reddy P, 2002 [94]	30	56	0.2**
Han KH, et al., 1998 [95]	34	56	4.5
Le Gal, et al., 1989 [71]	40	42	0.04**
Kennedy DO, 2003 [47]	15	1	0.2**
Kennedy DO, 2001 [96]	20	1	0.2–0.6**
D'Angelo L, et al., 1986 [61]	16	12	0.2**
Reay JL, 2006 [48]	30	1	0.2,0.4
Reay JL, 2005 [97]	30	1	0.2,0.4**

Sievenpiper JL, 2006 [98]	12	1	0,2,4,6
Gross D, 2002 [99]	92	84	0.2**
Caron, 2002 [102]	30	28	0.2**
Scaglione F, 1996 [101]	227	84	0.1**
Scaglione F, 1990 [102]	60	56	0.2**
Heo JH, 2008	**61**	**84**	**4.5, 9**
Oh KJ et al 2010	**32**	**(1)**	**3****

**** Standardized ginseng extract.**

B.5. Duration of the Study: Ginseng primarily exerts its action on fatigue via central effects (through neuroprotection, modulation of neurotransmission, central inhibition of inflammatory cytokines and improvement of cognition via direct action on the hippocampus). Pilot studies have suggested that these effects can be observed over a period of 4 weeks [102]. This period will allow enough time to observe improvements in the primary outcome of cancer related fatigue. A study period longer than 4 weeks would result in a number of patients dropping due to clinical complications, death or loss to follow-up.

B.6. Analytical Characterization and Validation of Ginseng Product

To date, several validated methods have been published on the identification and standardization of ginsenosides in *P. ginseng*, and other ginsengs, using various analytical techniques [103-107]. The method used for the Ginseng Evaluation Program, where more than 500 ginseng samples of various dosage forms were analyzed, had particularly good peak area to concentration linearity, using different dosage forms of ginseng, which was confirmed using spiking/recovery analyses [108].

Application of the Method: The four different ginseng extracts, Indena Ginseng Extract, Ginsana capsule, AHP botanical specimen, and Frontier brand ginseng were analyzed for ginsenoside Rb1 and Rg1 content. Table 2 shows the average of a total of six injections performed on two separate days, each day an extraction was performed immediately before the LC-MS experiments.

Test Substance[a]	Ginsenoside Rg_1[b,c]	Ginsenoside Rb_1[b,c]
Indena Ginseng Extract	0.12 %	0.19%
Ginsana Capsule	0.17%	0.12%
AHP Ginseng Botanical Specimen	0.22%	0.32%
Frontier Brand Ginseng	0.26%	0.58%

Table 2. Results of LC-MS analysis, average of three injections of each extraction performed on separate days. [a]One Ginsana capsule contains 100 mg of extract which is reported to be equivalent to approximately 500 mg of dried ginseng radix. Therefore, 500 mg was used for the ginseng plant extracts. [b]Both compounds were solubilized and diluted to six concentrations and injected in duplicate immediately prior to the injections of the test substances for each separate extraction. These percentages are the results of the averages of six injections on two different days. [c]The ratio of Rb_1 to Rg_1 is in the range of 1 to 3 for *P. ginseng* w here the range for *P. quinquefolius* is approximately 10.

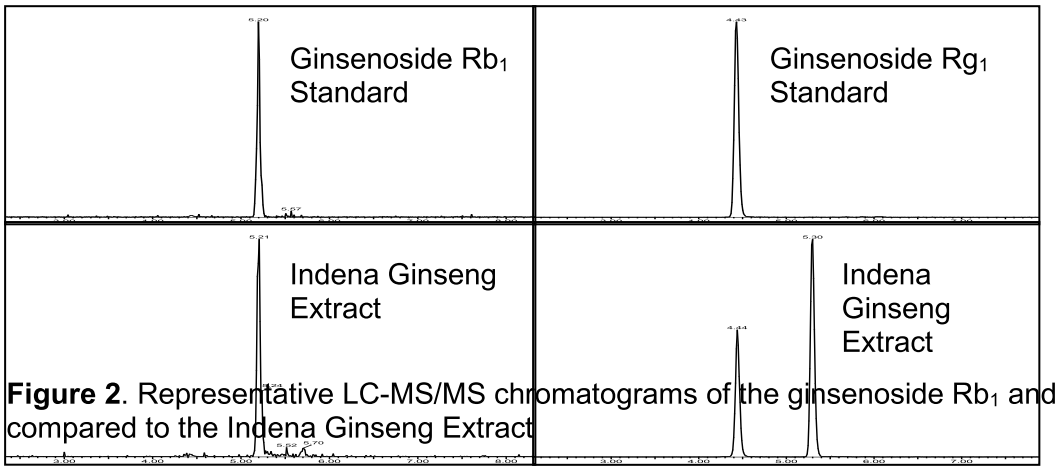


Figure 2. Representative LC-MS/MS chromatograms of the ginsenoside Rb_1 and Rg_1 standards compared to the Indena Ginseng Extract

B.7. Adverse Reactions (111)

P. ginseng is generally well-tolerated, and its adverse effects are mild and reversible. However, there are concerns that we will be monitoring for such as: Allergy/hypersensitivity: Known allergies/hypersensitivities exist to *Panax* species, their constituents, or to other members of the Araliaceae family. Cardiovascular: Arterial hypertension has been reported. However, one double-blind study failed to find any effect on blood pressure [110]. In 1979, an article was published in the Journal of the American Medical Association that claimed that people can become addicted to *P. ginseng* and experience blood pressure elevations, nervousness, sleeplessness, diarrhea, and hypersexuality, this condition was termed as ginseng abuse syndrome [111]. However, this report has since been thoroughly discredited and should no longer be taken seriously[112,113]. One case report and one double-blind trial suggest that P. ginseng can reduce the anticoagulant effects of Coumadin (warfarin) [114,115], but another trial did not find such an interaction [111]. The reason for this discrepancy is not clear. Psychiatric: Concomitant use of *P. ginseng* and the monoamine oxidase inhibitor phenelzine (Nardil) may result in manic-like symptoms [39,116]. Hepatotoxic effects: Ginseng may increase the toxicity of hepatotoxic agents. Ginseng has been well tolerated in prior studies(Barton etal 2009). However possible interactions with hepatoxic agents (Miller LG Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. Arch Intern Med 1998 Nov 9;158(20):2200) such as coumadin with reported increase in bleeding time. Hence we would monitor the PT/INR weekly for patients on coumadin and liver function test every 2 weeks (Total bilirubin </=1.5 mg/dL, and AST (SGOT) and ALT (SGPT) </=2 x ULN or </= 5 x ULN)if hepatic metastases are present or if patients are on potentially hepatoxic agents such as acetaminophen or statins. Patients with a history of hepatitis A, B and C will be excluded. Endocrine: There has been a few case reports of breast tenderness, postmenopausal vaginal bleeding, and menstrual abnormalities associated with Panax ginseng use [109,116]. Such side effects suggest that it has estrogenic properties. However, a large double-blind trial of P. ginseng found no estrogen-like effects [83] and a carefully designed in vitro study no estrogenic activity [120,121]. Ginseng decreased fasting blood glucose in both diabetic and non-diabetic patients and therefore combination use may lead to additive effects. Pregnancy and teratogeneity: Chinese tradition suggests that P. ginseng should not be used by pregnant or nursing mothers, and one animal study showed that ginseng use by a pregnant mother could cause birth defects [119-121]. In the proposed study, we plan to exclude patients with a psychiatric diagnosis, uncontrolled hypertension or arrhythmia, and diabetes; pregnant or lactating women; and patients taking anticoagulants, MAOIs [39,109], and tricyclic drugs. We will carefully monitor patients for adverse events and interactions with various medications, as described in Table 3.

Ginseng appears to be nontoxic, both in the short and long term, according to the results of studies in mice, rats, chickens, and dwarf pigs [120-124].

In summary, there are limited studies that used Panax ginseng for cancer related fatigue. the abstract of the results of a randomized study on cancer related fatigue in ASCO Proceeding 2008 shows it is well tolerated with activity against cancer related fatigue. However dose has not been mentioned. In prior trials in non-cancer patients, e.g for sexual dysfunction (see table 1) higher doses have been more effective. The common side effects at various doses have been used and generally well-tolerated, and its adverse effects are mild and reversible. The efficacy is more at higher doses as also shown in study by Barton etal 2009 Journal of Supportive care in cancer. A recent studies(125-127) shows some of the side effects reported include nervousness, insomnia, headache, skin eruptions, stomach upset, and increased menstrual bleeding and breast tenderness has been reported with the use of Panax ginseng. In our controlled clinical trial at MDACC we plan to closely monitor the effects of drug and placebo as outlined in the IRB protocol. We have also added the Dose Continuation, Modification and Interruption and trial stopping parameters.

B.9. Significance: Fatigue is a frequently debilitating symptom of cancer, as well as a common side effect of cancer treatment. At present, there are limited treatment options for the management of cancer-related fatigue (CRF). In clinical practice, more than 83% of patients use complementary and alternative medicines for treatment of cancer or symptoms. Ginseng is widely used in the United States as a

traditional medicine to improve overall energy and vitality, particularly during times of fatigue or stress. Results of pilot studies have indicated beneficial effects of P. ginseng on fatigue, primarily in the general population and in patients with cancer. However, P. ginseng's, preparation, duration of action, safety, tolerability, and possible mechanisms in CRF, have not been characterized. In addition, not all assessment tools used in previous studies were validated, and there was no attempt to understand the mechanism of action of P. ginseng using sophisticated laboratory correlates. The effects of P. ginseng on CRF and cytokine levels, and the role it plays in the treatment of CRF, must be thoroughly defined through randomized, controlled studies using updated, validated tools and laboratory correlates. Our findings will provide important preliminary data to determine the efficacy of P ginseng in alleviating cancer-related fatigue. It will also provide information regarding safety, tolerability and possible mechanisms of action, including its effect on physical function, which are currently considered to be important components in the causation of this distressing symptom.

C. RESEARCH DESIGN AND METHODS

C.1. Study Design: This is a 2 phase trial, (1) Phase I: an initial non dose escalating phase to evaluate dose limiting toxicity (2) Phase II a second phase- RCT double blind phase and (3) Both phases will have an open labeled phase. Patients in both Phase I or II may continue the ginseng in the open labeled extension phase if there are no grade 2 or more toxicity as per CTRC criteria as determined by the PI.

C.2. Ginseng Product: *Panax ginseng*: The drug used for this clinical trial is an Standardized *Panax ginseng* root extract (supplied by Indena, S.P.A., Milan Italy compliant with NCCAM product quality [91] (See APPENDIX B for drug and placebo information and letter of support), has been standardized for total ginsenosides and ginsenoside ratio of the major ginsenosides. The matching placebo will use colored capsules for similar appearance since ginseng extract has little or no odor that needs blinding, and it will include the inactive excipient methylcellulose.

C.3. Subjects

C.3.2. Eligibility Requirements

C.3.2.1. Inclusion Criteria

1. All patients with a histological diagnosis of cancer.
2. Rate fatigue on a numerical scale during the previous 24 hours as $\geq$ 4 on a 0 to 10 scale (0 = no fatigue and 10 = worst possible fatigue).
3. Describe fatigue as being present every day for most of the day for a minimum of 2 weeks.
4. Memorial delirum assessment scale </= 13.
5. Are 18 years or older.
6. Hemoglobin level of $\geq$8 g/dL within 2 weeks of enrollment. If the patient has not had blood drawn for a hemoglobin level in the previous two weeks, one will be performed to determine eligibility. Patients with a hemoglobin level <9g/dL will be evaluated for treatment of anemia.
7. Able to understand and sign the informed consent.
8. No concurrent use of chronic systemic steroids (defined as currently on more than 1 week of treatment).
9. Controlled pain and depression symptoms, if present (defined as no change in the Morphine equivalent dose of 30% or change in the dose of antidepressant medication in the past 2 weeks)
10. Patients should have a Zubrod </= 2.
11. All patients who are receiving chemotherapy and/or radiation therapy are eligible for study if they have completed at least one cycle of chemotherapy or targeted therapy, or > 1 week of radiation therapy, and if they have been approved to go on study by their primary oncologist. The PI/designated research staff of this study will obtain and document approval from the primary oncologist and principal investigator of the clinical trial in case the patient is on another clinical trial as referenced in the patient's study documents.
12. Negative pregnancy test for women of childbearing potential, as defined by intact uterus and ovaries, and a history of menses within the last 12 months. Pregnancy test to be performed no greater than 14 days prior to consent in study. In cases of women with elevated b-HCG, these candidates will be eligible to participate so long as the level of b-HCG is not consistent with

pregnancy. Women of childbearing potential need to be on or use contraception, or be abstinent during the study period. Their male partners must also use contraception (condom) or maintain abstinence.
Birth controls specifications: Women who are able to become pregnant must use birth control during the study and for 30 days after the last ginseng/placebo dose.

Acceptable forms of birth control include barrier methods (such as condom or diaphragm) with spermicide.

C.3.2.2. Exclusion Criteria

1. Major contraindication to ginseng: allergy/hypersensitivity to *Panax* species or their constituents (history of arrhythmias, agitation, or motor tics, or severe angina pectoris).
2. Currently taking ginseng, methylphenidate or modafinil or have taken it within the previous 10 days.
3. Inability to complete the baseline assessment forms or to understand the recommendations for participation in the study.
4. Currently with a diagnosis of major depression, manic depressive disorder, obsessive-compulsive disorder, or schizophrenia).
5. Symptomatic tachycardia and uncontrolled hypertension (determined to be clinically significant by the PI).
6. Currently receiving phenobarbital, diphenylhydantione, primidone, phenylbutazone, MAOIs, clonidine and tricyclic antidepressant drugs
7. Uncontrolled diabetes mellitus as defined by a random blood sugar of >200mg/dl not being monitored by their primary care physician.
8. No concurrent full dose anticoagulant therapy. </= 1 mg/day of coumadin for preventing catheter clots allowed.
9. History of hepatitis A, B and C.
10. Women who are nursing.

C.4. Rationale for Different Tumor types:

On the basis of clinical trials of methylphenidate [127,128,130,139], donepezil [129,130] and fish oil [132], in the treatment of cancer related fatigue by our group and studies by other groups [140-144] the frequency, severity and mechanisms of fatigue in cancer patients with different tumor types are largely the same. By including patients having fatigue with different tumor types, we will obtain a more representative distribution of patients in terms of age, sex and behavioral than we would in a study of patients with a single tumor type. Despite the different tumor type the expression of fatigue is a result of common pathophysiology (such as dysregulation of cytokines such IL-1β, IL-6, IL-10 and TNF-α) in patients with cancer. As there are no cancer type-specific studies using ginseng for cancer related fatigue, we would use the preliminary data obtained from the responses to individual cancer types in this study. Future cancer specific studies will be designed based on these results. In addition, we have added collaborators from other departments and clinics who are currently treating patients with these diseases.

C.5. Randomization

Patients will be randomly assigned to one of the two treatment arms. The randomization schema will be based on parameters input into RANLST, a randomization program developed at UTMD Anderson and supported by an NCI grant.

C.6. Clinical Trial Design and Treatment Plan:

This study will have (1) Phase I: an initial non dose escalating phase to evaluate dose limiting toxicity. A total 30 evaluable patients will be enrolled in this phase. After study completion of the 30 evaluable patients (2) Phase II a second phase- RCT double blind phase will be started and (3) Both phases will have an open labeled phase. Patients in both Phase I or II may continue the ginseng in the open labeled extension phase if there are no grade 2 or more toxicity as per CTRC criteria as determined by the PI. A

total of 158 eligible patients will be enrolled in both phases of the trial (30 evaluable in phase I + 128 in phase II). (See Study Design Fig. 6).

Evaluable patients will be defined as any patient enrolled on the study that has taken at least one dose of treatment (i.e., either ginseng or placebo), making them available for toxicity and response.

C.6.1. Double-Blind Phase Dosing Patients will be randomized to one of two experimental groups receiving the treatments detailed below.

- The placebo group (**Arm 1**), will receive oral placebo twice daily for 29 days.
- The Panax ginseng group (**Arm 2**) will receive ginseng capsules 400 mg twice daily for 29 days.

Unblinding Procedure:

1. The Statistician and the investigational pharmacist will have access to the codes/assignments.
2. The codes will be revealed only If there is a safety issue and the treating physician needs to be aware of the treatment assignment.
3. The PI should be contacted regarding and give approval for un-blinding
4. The Investigator/research team must inform the IND Office when un-blinding occurs.

C.6.2. Open-Label extension Phase

The intervention phase of Phase I and II parts of the study will be followed by an open-label extension phase that will begin after the assessment on Day 29. Assessments of fatigue, physical activity, and psychosocial functioning will be conducted at baseline, day 15 and day 29. On Day 29, the study will be completed and patients will be given the option of continuing on an open label basis, Panax ginseng 800 mg per day, will be provided they have tolerated the double-blind phase without moderate to severe toxicity as per NCI CTC AE V4 criteria . All patients will be taken off the study on day 57. Patients will be followed for upto 30 days after the last dose of Panax ginseng.
“Baseline” evaluations, PE, history should be completed within 2 weeks prior to registration or 1 week prior to start of study drug(Table 3). The Drug compliance will be monitored with a pill diary and with weekly calls/ or in person meeting the patient by RN along with Toxicity evaluation (See Table 3). Toxicity evaluation, symptom assessment and medication review will include assessment toxicity using NCI CTCAE V4 criteria on Days 8, 15, 21, 29, 36, 43, and 57 (Table 3) (all +/- 3 days). Adverse events (including event name, grade, start/stop date and attribution) will be entered into PDMS/CORe, which will serve as the source documentation for adverse events. The Principal Investigator or physician designee will verify the attribution assigned in PDMS/CORe by signing the PDMS/CORe adverse events printout at the end of protocol treatment. PDMS/CORe will be used as the electronic case report form for this protocol.
The unused drug returned will be documented in the shadow chart and destroyed as per institutional policy.

CBC, Electrolytes, Total bilirubin, and AST (SGOT) and ALT (SGPT will be done at Baseline, CBC and Electrolytes will be done at Day 15+/- 3days and Day 29+/- 3days. We would monitor the PT/INR weekly for patients on coumadin and liver function test every 2 weeks (Total bilirubin, and AST (SGOT) and ALT (SGPT) if hepatic metastases are present or if patients are on potentially hepatoxic agents such as acetaminophen or statins. Laboratory studies will be performed at baseline, day 15, and day 29. Hematology and chemistry blood collection will be performed on the expanded open label cohort of patients at Day 57 or conclusion of P. ginseng. Patient can have the labs drawn at outside facility. The research nurse will obtain results from outside labs via fax, or email. Patients entered on the open label phase will be followed until their respective study conclusion.

Day 15, 29, and 57 safety labs and Day 15 and 29 optional research blood will be collected only if patient returns to MDACC for the follow-up visits.

Dose Continuation, Modification and Interruption

II. Dose Continuation, Modification and Interruption

Subjects will be evaluated for AEs with the NCI CTCAE v4.0 as a guide for the grading of severity.

Table A outlines Panax ginseng/placebo dose reduction steps

Table A: Panax ginseng/ placebo Dose Reduction Steps	
Starting Dose	400mg capsule or identical placebo orally BID for 28 days
Dose Level –1	400 mg daily or identical placebo for rest of the treatment phase (up to day 29)

INSTRUCTION FOR INITIATION OF A WEEK 3, AND OPEN LABEL

Prior to initiation of treatment of day 15, and open label phase (Day 29) the patient should have:

We would monitor the PT/INR weekly for patients on coumadin and liver function test every 2 weeks[day 15 +/-3 days, and day 29+/-3 days (Total bilirubin </=1.5 mg/dL, and AST (SGOT) and ALT (SGPT) </=2 x ULN or </= 5 x ULN)if hepatic metastases are present or if patients are on potentially hepatoxic agents such as acetaminophen or statins.

- Any Panax ginseng-related or identical placebo related allergic reaction/hypersensitivity that may have occurred has resolved to ≤ grade 1 severity;

- Any other Panax ginseng-related or identical placebo -related adverse event that may have occurred has resolved to ≤ grade 2 severity.

If these conditions are not met on Day 15 or Day 29 (all +/- 3 days), the subject will be evaluated weekly and Panax ginseng will not be initiated until the toxicity has resolved as described above. The patient can be off the drug for a total 1 week before being removed from the treatment phase of the study.

INSTRUCTIONS FOR DOSE MODIFICATIONS OR INTERRUPTION DURING A TREATMENT PHASE.

NCI CTC 4 Toxicity Grade	Day 2- 57
Grade≥ 2 neutropenia related to Panax ginseng or placebo associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Discontinue Panax ginseng study drug or identical placebo.
Thrombocytopenia Panax ginseng or placebo ≥Grade 2 (platelet count < 50,000/mm³)	• Discontinue Panax ginseng study drug or identical placebo
Steven Johnson syndrome	• Discontinue Panax ginseng study drug or identical placebo
Desquamating (blistering) rash- any Grade	• Discontinue Panax ginseng study drug or identical placebo.
Rash, Erythema multiforme ≥ ≥Grade 2	• Discontinue Panax ginseng study drug or identical placebo.
Hypertension, Hypotension, cardiac arrhythmia ≥Grade 2 ≥ Grade 3	Hold (interrupt) dose, Up to one week before taking off study Follow at least weekly. If the toxicity resolves to ≤ grade 1 restart dose at (400mg) level and continue the study medication with continued monitoring as prescribed in the protocol. If the patient has repeat cardiac arrhythmias ≥ Grade 2. He will be discontinued from the study medication and monitored. Discontinue Panax ginseng study drug or identical placebo.
Allergic reaction or hypersensitivity ≥Grade 2 >/= Grade 4	• Hold (interrupt) dose, Up to one week before taking off study • Follow at least weekly. • If the toxicity resolves to ≤ grade 1 restart dose at (400mg) level and continue the study medication with continued monitoring as prescribed in the protocol. • If the patient has repeat ≥ Grade 2 allergic or hypersensitivity reaction, he will be discontinued from the study medication and monitored. • Discontinue Panax ginseng study drug or identical placebo.
	•

NCI CTC 4 Toxicity Grade	Day 2- 57
Any Other non-hematologic toxicity assessed as Panax ginseng study drug or identical placebo - related ≥ Grade 2 including insomnia, anxiety, restlessness, behavioral change, dizziness, vertigo, tachycardia, diahhrea, nausea/vomitting, headache, increased menstrual bleeding and breast tenderness	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 restart dose at (400mg) level and continue the study medication with continued monitoring as prescribed in the protocol. • If the patient has repeat ≥ Grade 2 non-hematological toxicity, they will be discontinued from the study medication and monitored.

III. Discontinuation of Study Treatment

Treatment will continue until Day 29±3 and Day 57±3 for participants eligible for the open label phase.

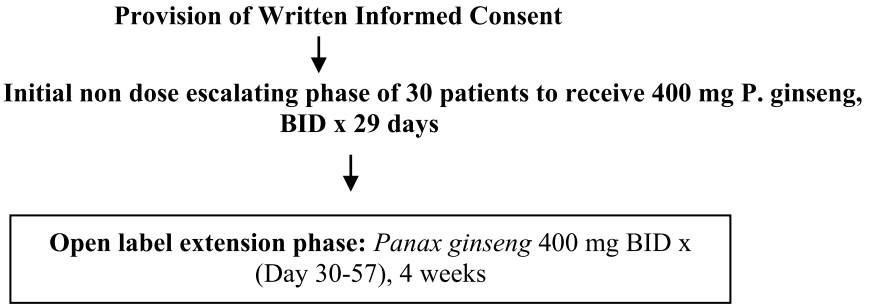
Treatment with study drug is to be discontinued when any of the following occurs:

- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
- Suspected pregnancy

Major violation will be determined by the PI. Major violation will include lack of consent, lack of safety laboratory tests. These will be reported to IRB and FDA in a timely fashion.

Figure 6. Study Design

Phase I(1st 30 patients)



Phase II

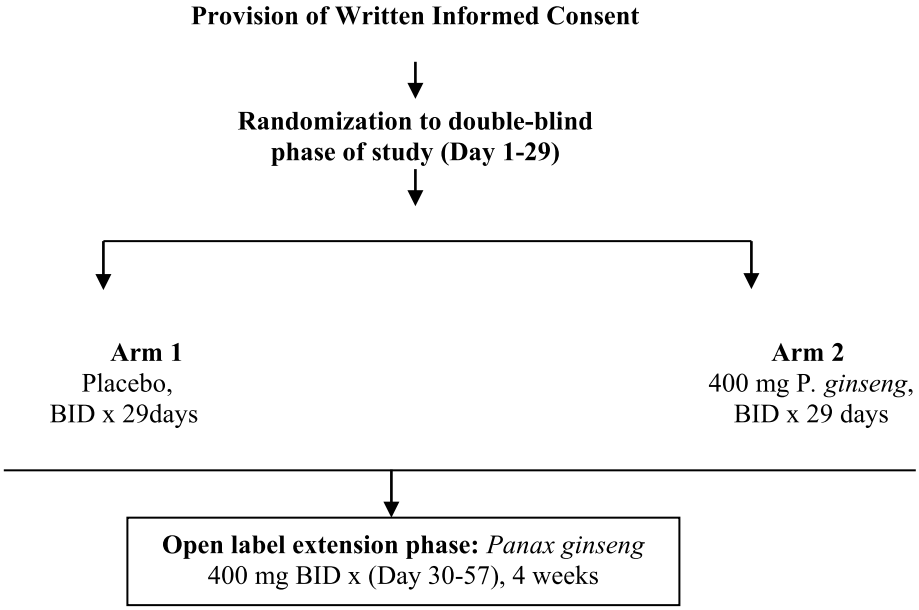


Table 3. Study Assessments

ASSESSMENTS	Baseline	Day 8 (± 3)Ph#	Day 15 (± 3)	Day 21 (± 3)Ph#	Day 29 (± 3)	Day 36 (± 3) Ph#	Day 43 (± 3)Ph#	Day 57 (± 3)
Medical History	X							
Physical Examination	X							
Zubrod Score	X							
Medication Review	X	X	X	X	X	X	X	X
Symptom and QoL Assessment								
ESAS	X	X	X	X	X	X	X	X
HADS	X		X		X			X
FACT-G &FACIT-F subscale	X		X		X			X
SDMT	X		X		X			X
GSE**					X			X
Physical Activity								
6 minute walk test	X		X		X			X
Hand grip Strength and Endurance test	X		X		X			X
Hematology/ Chemistry*	X		X		X			X
Pregnancy Test@	X							
Optional Blood Draws	X		X		X			
Toxicity Evaluation	X	X	X	X	X	X	X	X

* CBC, Electrolytes, Total bilirubin, and AST (SGOT) and ALT (SGPT will be done at Baseline, CBC and Electrolytes will be done at Day 15+/- 3days and Day 29+/- 3days. We would monitor the PT/INR weekly for patients on coumadin and liver function test every 2 weeks (Total bilirubin, and AST (SGOT) and ALT (SGPT) if hepatic metastases are present or if patients are on potentially hepatoxic agents such as acetaminophen or statins.

**GSE – Global symptom evaluation
#Assessment via telephone or in person
@ Pregnancy test to be performed no greater than 14 days prior to consent in study.

If patients are unable return to the clinic for any of the scheduled assessment days (Day 15, Day 29, Day 36, and/or Day 57), we will contact the patient via telephone to complete the symptom and quality of life assessments (ESAS, HADS, FACT-G, FACIT-F, and GSE). If contacted by phone, then physical assessments will not be performed.

Adverse events will be captured according to the recommended AE recording guidelines for a Phase II protocol.

C.7. Symptom Assessment

C.7.1. Demographic variables

Demographic variables will include patient self-reported birth date, sex, marital status, ethnicity, education, and job status, primary cancer, cancer treatment within the last year, surgery, chemotherapy, immunotherapy or radiotherapy, and medications including opioid dosage. **(APPENDIX P).** Appendix P also includes tracking the baseline labs ordered and an off study note that will be completed once the patient has been taken off study.

C.7.2.Symptom assessment (see Table 3)

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (including the Functional Assessment of Chronic Illness-General (FACT-G) and Fatigue subscales), Hospital Anxiety and Depression Inventory (HADS), Edmonton Symptom Assessment System (ESAS), Symptom Digit Modalities Test (SDMT) and Six minute walk test, will be used assess outcomes.

Adherence: Patients with similar characteristics to those of patients we will admit to the study have demonstrated strong adherence to assessments of the same duration in studies conducted by our group [128,129,137,138]. These assessment tools have been validated and are reliable for use in the collection and analysis of data. Also patients in this study with not undertake time intensive radiological tests such as MRI'S or drug pharmacokinetic studies which are a common part of clinical trials. This would enable help in completion and minimize attrition.

C.7.2.1. Outcome Measures

Specific aim# 1. **To explore effects of 800mg of P. ginseng as compared to placebo on cancer-related fatigue as determined by FACIT-F at the end of 29 days.** We hypothesize that patients randomized to receive P. ginseng will demonstrate greater improvement in CRF than Placebo. To prove this hypothesis we will measure the intensity of fatigue using the following instruments: FACIT-F (145) Although two measures used to assess fatigue were the (1) FACIT-F and (2) ESAS, the primary end point was the FACIT-F score. The FACIT-F is a well-validated quality-of-life instrument widely used for the multidimensional assessment of cancer-related fatigue in clinical trials. (147) It consists of 27 general quality-of-life questions divided into four domains (physical, social, emotional, and functional), plus a 13-item fatigue subscore. This 13-item fatigue subscore was the primary outcome of our study. The patient rates the intensity of fatigue and its related symptoms on a scale of 0 to 4. The total score ranged between 0 and 52, with higher scores denoting less fatigue. In a recent metanalysis of pharmacological treatments of cancer related fatigue (146) of 27 eligible treatments trials that were selected, FACIT-F was used a primary end point in majority of them. It has been also been used in prior fatigue treatment studies by our team. We have currently have 3 (NIH) R01 projects in our team using FACIT-F tool and we have a large database with FACIT-F tool. Our research team is very familiar using FACIT-F tool and this will allow us to compare results with those of other interventions in our database (such as Methylphenidate, Nursing Telephone intervention for treatment of fatigue). Test-retest reliability coefficients for the fatigue subscale are 0.84– 0.90. This scale has also demonstrated strong internal consistency (α=0.93-0.95).

Specific aim# A.2

- To explore its effect on physical activity as measured by six minute walk test.
- To explore its impact on quality of life-related variables: mood (HADS), and quality of life domains (FACT-G)) in these patients.
- To explore its side effects and tolerability of *P. ginseng* in these patients.
- To estimate the proportion of patients experiencing clinical benefit in each arm and to compare these proportions between arms

We hypothesize that patients randomized to receive P. ginseng will demonstrate greater improvement in depression, anxiety, and overall symptom burden, as compared to placebo. In order to achieve these secondary aims we will assess depression and anxiety using HADS, overall symptom burden using ESAS, Physical activity by Hand grip strength and hand grip endurance test, and quality of life using FACT-G.. Depression and Anxiety. Depression and anxiety symptoms will be assessed using the 14-item HADS [147] questionnaire. This questionnaire asks patients to underline the statement that most closely matches how they have been feeling in the previous week. This questionnaire has been found to be valid and reliable in a number of clinical situations and has been widely used in medically ill patients. Other Common Symptoms. The ESAS [135,136] measures 10 common symptoms in the past 24 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well-being) during the previous 24 hours; This questionnaire has been found to valid and reliable in cancer populations. Neurocognitive function will be measured using the Symbol Digits Modalities Test

(SDMT). This is a useful diagnostic tool measuring clerical speed, visual search and memory, fine motor control and concentration. (Turner M. Symbol Digit Modalities Test. Staines: Dyslexia Institute. 1999.)
Physical Activity: a) The Six-Minute walk test will be used to assess physical function and has been recommended by the American Thoracic Society (ATS) as an objective measure of functional capacity [148]. This test has been found to be an objective measure of functional capacity in patients with chronic respiratory conditions, fibromyalgia, stroke, and cancer. Our group has used this methodology in the assessment of fatigue and dyspnea. Our previous study demonstrated that 6-minute walk in patients with fatigue and dyspnea related to lung cancer was well tolerated. All 33 (100%) patients were able to tolerate two episodes of 6-minute walks within half hour [149]**.** Assessment will occur at baseline, day 29 and Day 57.

Hand Grip Strength and Endurance Test: The hand grip strength and endurance test will be administered at baseline, Day 15, 29, and 57. The purpose of this test is to measure the maximum isometric strength of the hand and forearm muscles. The patient will hold the dynamometer in the hand to be tested, with the arm at a right angle and the elbow by the side of the body. The handle of the dynamometer is adjusted if required - the base should rest on the first metacarpal (heel of palm), while the handle should rest on the middle of four fingers. When ready, the patient squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 seconds. No other body movement is allowed. The patient will be strongly encouraged to give a maximum effort.

Blood will be collected from consenting patients (optional procedures) for future investigational studies to explore ginseng's effect on induced monocyte inflammatory cytokines (IL-1β, IL-6, IL-10 and TNF-α) production and the serum levels of these cytokines (IL-1β, IL-6, IL-10 and TNF-α) in cancer patients. The blood samples will be stored in a -80°C freezer for future studies on cytokine levels in patients with cancer and cancer-related fatigue[152]. Optional procedure lab draws will be documented in a sample log that will include the data of blood draw, signature of person obtaining blood sample as well as the storage conditions and location (-80 degree freezer in laboratory of Dr. James Reuben).

Global Symptom Evaluation. This instrument is to estimate the minimal important difference in symptoms before treatment and after treatment. Patients will be asked about their symptoms (worse, about the same, or better) after starting new medication. If their answer is better, patients will be asked to rate how much better their symptoms are (almost the same, hardly any better at all, a little better, somewhat better, moderately better, a good deal better, a great deal better, a very great deal better). If their answer is worse, patients will be asked to rate how much worse their symptoms are (almost the same, hardly worse at all, a little worse, somewhat worse, moderately worse, a good deal worse, a great deal worse, a very great deal worse). This evaluation will be performed on day 29 and day 57.
Toxicity Evaluation. On Day 29, the study will be completed and patients will be given the option of continuing on an open label basis, Panax ginseng 800 mg per day, will be provided they have tolerated the double-blind phase without moderate to severe toxicity as per NCI CTCAE V4 criteria. Toxicities will be evaluated using the NCI CTCAE Version 4 Criteria (Appendix A) on Days 8, 15, 21, 29, 36, 43 and 57 (all +/- 3 days). Adverse event (including event name, grade, start/stop date and attribution) will be documented in the medical record and entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol.
The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial

C.8 Serious Adverse Events Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Adverse events will be captured according to the recommended AE recording guidelines for a Phase II protocol.

Recommended Adverse Event Recording Guidelines						
Attribution	**Grade 1**	**Grade 2**	**Grade 3**		**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II		Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II		Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III		Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III		Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III		Phase I Phase II Phase III	Phase I Phase II Phase III

Optional Procedures (Blood Draws): Serum and peripheral blood lymphocytes will be an optional procedure for all eligible patients. If the patient provides consent for the optional blood draw and serum is collected, the serum will be stored. On completion of the study, a future study will look at the change in levels of serum cytokines (IL-1β, IL-6, IL-10, and TNF-α) and cytokines in the induced monocytes (IL-1β, IL-6, IL-10, and TNF-α) to see if there is a correlation with the proportion of patients with decreased fatigue and with those who have no decrease in fatigue. *Methods:* Plasma will be harvested from blood specimens and stored frozen at –80°C for cytokine batch analyses at a later date. The assays that would be performed in the future would require as little as 50 μL of serum or plasma. Serum cytokines levels of IL-1β, IL-6, IL-10, and TNF-α would be analyzed in a future study for samples collected at baseline, Day 15 and 29.

C.9. Statistical Analysis

This is a preliminary study to explore the efficacy of P. ginseng in reducing fatigue as measured by the Functional Assessment of Cancer Therapy- Fatigue (FACIT-F) subscale. Because this Panax ginseng has not been previously evaluated in cancer related fatigue, we will implement this study in two phases. In the first phase(initial non dose escalating phase), we will enroll up to 30 patients in the Arm 2 (treatment arm); patients will not be enrolled in the placebo arm. Recruitment will be halted until these original 30 patients can be evaluated for DLTs. In the second, main phase patients will be randomized to receive either Panax ginseng or placebo. As a

primary analysis, we will assess the level of fatigue at baseline and after 29 days to determine group differences in fatigue changes over time using analysis of variance. This analysis will test for differences between groups, differences over time, and a group by time interaction. We will also perform a repeated measures analysis by group using all available time points (for the FACIT-F fatigue subscale at baseline, day 15 and day 29). This analysis will test for differences between groups, differences over time, a group by time interaction, and trends over time. For all analyses of continuous variables, if the data are not approximately normally distributed, we will either use a nonparametric equivalent of the statistical test or we will transform the variable to achieve approximate normality. The design of the study is intent to treat, i.e., it is our aim to analyze anyone who received at least a single dose for both toxicity and response. Response would be considered clinical beneficial if they improve 3.5 points on the FACIT- F fatigue subscale at day 29 or day 15 (if day 29 is unavailable). Patient who have not completed at least day 15 would be considered inevaluable for consideration of clinical benefit.

Pilot Analysis:
We will summarize patient characteristics of all patients enrolled in the pilot study. Means and standard deviation or medians and IQRs will be calculated. We will also perform exploratory analyses on the changes in FACIT-F subscale (primary outcome measure) from baseline to Day 29 and baseline to Day 57. Similar analysis will be conducted for the secondary outcomes (FACT-G, ESAS symptoms, HADS, SDMT, six- minute walk test, Borg Scale, GSE and Hand Grip Strength and Endurance Test). Based on whether the data is normally distributed (Shapiro- Wilk test) we will use paired t-tests or Wilcoxon Ranked Sum tests. We will also summarize fatigue scores, other secondary outcomes at each point in time and the frequency and type of side effects as determined by NCI CTCAE V4 criteria.

Safety Monitoring
Safety Monitoring
Because this Panax ginseng has not been previously evaluated in cancer related fatigue, we will implement this study in two phases and we will utilize early stopping rules for dose-limiting toxicities (DLTs) for 30 patients in the treatment arm (Arm 2, Panax ginseng 800mg/day) before the main phase of the study begins. A DLT is defined as any Grade 3 or 4 toxicity that is attributable to the treatment regimen.

In the first phase, we will enroll up to 30 evaluable patients in the Arm 2 (treatment arm); patients will not be enrolled in the placebo arm. Recruitment for the main study will be delayed until these original 30 patients are evaluated for DLTs. We will base early stopping rules on a method proposed by Thall et al., (160) and using the Multc99 software from the Department of Biostatistics.

To ensure that the true DLT rate is sufficiently low, we will terminate the study early if the probability that the estimated toxicity rate is greater than 10% (given the results) is greater than 0.95. We assume a prior of Beta (0.1,0.9) in these calculations. The study will be stopped early if (# patients with DLT) / (# patients evaluated) >= 3/6, 4/10, 5/16, 6/22, or 7/29.

The table below shows operating characteristics given differing true toxicity rates based on 10000 simulations for each row:

Operating Characteristics for first phase early stopping rule (based on DLT)

True DLT rate	Probability Early Stopping	Achieved Sample Size 25^{th}, 50^{th}, 75^{th} percentiles		
1%	<0.0001	30	30	30

3%	0.002	30	30	30
5%	0.013	30	30	30
8%	0.053	30	30	30
10%	0.116	30	30	30
15%	0.324	20	30	30
20%	0.597	9	21	30
25%	0.791	8	14	27
30%	0.917	6	9	17
40%	0.993	6	7	9

During the second phase of the study, the DSMB will meet to assess toxicity in an unblinded fashion at defined intervals (annual review) and will terminate the study if the incidence of DLT on either arm is judged by the DSMB to be excessive.
Power Considerations: There are no randomized controlled trials on P.ginseng for the management of CRF. The only intervention with Level I evidence for effectiveness in CRF is exercise. Among the most important clinical trials conducted on the intervention are those of Segal etal [154-156]. They have determined the clinically important difference in fatigue as a result of intervention as compared to placebo. Since these two studies used FACIT-F (our primary outcome) we have used these studies for power/sample size calculation. We postulate that if P.ginseng is an effective intervention we will observe a difference in response at Day 29(primary end point) similar and higher to those observed in the Exercise studies. We plan to include 50 evaluable patients per group. If we assume that our dropout rate will be no higher than 20%, we will recruit 64 patients into each group, for a total of 128 patients. As we could find no other published studies about the use of Panax ginseng in cancer patients, we base our sample size estimate on previous research in resistance exercise training [154]. This study found that the difference between groups in changes in the FACIT_F subscale at 24 weeks was 4.78, significant at p=0.002, and was powered to detect a difference of 3.5 points based on a similar study in exercise resistance [155] that found standard deviations in difference scores over 12 weeks of 5.8. Studies such as Cella et al, 2002[156], state that differences of 3-5 points or more on the FACIT-F subscale are clinically important differences. If we assume a standard deviation of 5.8 in difference scores, with 50 evaluable patients per group we will be able to detect differences as small as 3.3 or larger with a two-sided significance level of 0.05 and 80% power. With standard deviations in difference scores as large as 8.8, we will still be able to detect differences of 5 points or greater.

Evaluable patients will be defined as any patient enrolled on the study that has taken at least one dose of treatment (i.e., either ginseng or placebo), making them available for toxicity and response. Although we expect dropouts (20% of 128 patients) the primary analysis will not include dropouts, but a secondary analysis would carry forward the last known FACIT-F score for those patients who had received at least one dose.

Yearly interim analyses will be conducted by the biostatistician and the results will be presented to the MDACC DSMB office. Results will be presented overall and by arm retaining the blinding as to arm assignment unless requested to reveal arm assignment by the DSMB (usually only made if one or both of the arms show a significantly less than expected efficacy or toxicity). In that case the statistician will reveal the arm assignments to the DSMB. The PI and other collaborators (other than the statistical collaborator) will remain blinded as to the arm assignments of patients.

As a part of each interim analysis, we will determine if either arm has significantly more occurrences of greater than grade 2 adverse events ($p<0.05$) as compared to each other. If this is found it will be reported to the DSMB and the study may be terminated early.

A formal interim analysis will be conducted when a total of 50 evaluable patients (one-half of the total number of evaluable patients) have been evaluated for 29 days. This interim analysis will allow for the early termination of the study in light of evidence that patients in either arm improve significantly than the other arm (early stopping due to superiority) or that patients in the two arms have similar improvement (early stopping due to futility). In order to provide for an overall two-sided significance level of approximately 0.05 for the study, the interim analysis will have a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule for both tests (EaSt, version 5, Cytel Software Corporation). The decision boundaries for the interim test will be to accept the null hypothesis of no treatment difference (futility) if the test statistic $|Z| < 0.348$ ($p > 0.73$), reject the null hypothesis if $|Z| > 2.96$ ($p < 0.003$), or otherwise continue the trial. The final test cut-off will be to reject the null hypothesis if $|Z| > 1.95$ ($p < 0.051$).

Secondary Analyses: We will compare the physical activity levels of participants in the two groups as measured by the hand grip dynamometer. We will also test the quality of life variables with the HADS and FACT-G tests. As each of these variables is also continuous and measured at the same points in time, we will determine the relationship of each of these variables to fatigue and analyze the data using repeated measures analyses as described above, testing for differences between groups, over time, and a time by group interaction. If several variables appear to be significantly related to fatigue, we will also perform multivariate analyses to determine the best predictors of fatigue as measured by the FACIT-F subscale. We will also determine relationships between daily or weekly fatigue, symptom data, and daily measures of sleep duration and fragmentation by determining correlation coefficients within time periods. Exploratory analyses of all subscale scores will be performed after the primary endpoint has been analyzed.

Summary information on the global symptom evaluation by group will also be provided at each of the assessed time points. Differences in distributions between groups will be analyzed using a chi-square analysis.

On an exploratory basis, we will also investigate whether or not different results were found for patients with different types of cancer, primarily using descriptive statistics. We do not expect to find statistical significance due to the low numbers of patients in each cancer type, but if we do find trends that appear to be significant, we will use this information to inform a future study. Additionally as a part of exploratory analysis, we will use Pearson chi-squared tests to compare the proportion of patients experiencing clinical benefit between each arm.

Information about toxic effects and tolerability will be summarized at each dose level. Safety assessments including hematology and chemistry assessments and toxicity evaluations will be made throughout the study (see Table 3).

For future investigational studies, analyses of the relationships between inflammatory cytokines and fatigue will also be performed using correlation analyses. The cytokines (serum and Induced monocyte) we will explore in future analyses include IL-1β, IL-6, IL-10 and TNF-α. Information on cytokines and fatigue will be available at baseline, day 15 and day 29. We plan to explore the correlations between cytokines and fatigue within each time point and between time points.

D.10. Future Studies: The exploratory data gathered will be used to design a larger trial that will also allow for longer longitudinal follow-up of patients to determine the onset and duration of response;

determine whether response to ginseng occurs more frequently in patients with certain primary tumors or disease stages; and to determine adherence to assessments using different tools and timing of different evaluations. A larger study will also allow us to better characterize the role of cytokines versus direct central effects. The preliminary data obtained will allow us to design appropriate larger trials from the important information obtained regarding response, adherence to assessments using different tools, and timing of different evaluations. The trends observed for the secondary objectives of this preliminary study will allow us to conduct larger clinical trials and apply for future grant applications. The associations between symptom interventions as assessed using validated symptom assessment tools, objective measures such as Hand grip strength test and actigraphy, and levels of cytokines including monocyte induction, will justify for future fatigue studies.

D.11. Protection of Human subjects: We will obtain authorization for use and disclosure of Protected Health Information (PHI) from patients. This will be included in the written informed consent. We will follow The Health Insurance Portability and Accountability Act (HIPAA) guidelines during the study based on the following 3 criteria: 1) All research staff have completed research training concerning confidentiality of protected health information. Patient's name, social security number and other patient identifiers will not be used for data collection. Only protocol accession numbers will be used in data collection. The principal investigator will keep the collected data in a locked file cabinet; 2) Data collected for this study will be retained for 2 years after publication of the research and then it will be destroyed by a mechanic shredder; 3) The data will be used for this study and may be disclosed for use on other studies that have IRB-approval to access this data. Only the PI, the project manager, the research nurse and the data manager will have access to the data. The data will not be disclosed to any other parties without an IRB-approved protocol and appropriate IRB-approved consent/authorization or waiver.

E. REFERENCES

1. Paice J. Assessment of symptom clusters in people with cancer. Journal of the National Cancer Institute Monographs No. 32, 2004; 98-102
2. Minasian LM, O'Mara AM, Reeve BB, et al.,Health-related quality of life and symptom management research sponsored by the National Cancer Institute. J Clin Oncol. 2007; 25(32):5128-32.
3. Trask PC, Griffith KA. The identification of empirically derived cancer patient subgroups using psychosocial variables. J Psychosom Res. 2004; 57: 287-95.
4. Cleeland CS. Pain and symptom burden: lessons from patients with cancer. Presentation at the American Pain Society Meeting. Baltimore, MD, March 14-17, 2002; American Pain Society, Glenview, IL.
5. National Comprehensive Cancer Network Practice Guidelines. Cancer-Related Fatigue Panel 2006 Guidelines. Rockledge, PA: National Comprehensive Cancer Network; March 2006.
6. Cella D, Peterman A, et al. Progress towards guidelines for the management of fatigue. Oncology. 1998;12: 369-377.
7. Portenoy RK, Itri L. Cancer-related fatigue. Oncologist. 1999; 4:1-10.
8. Smets EM, Garssen B, et al. Fatigue in cancer patients. Br J Cancer. 1993; 68:220-224.

9. Cella D, Davis K, et al. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. J Clin Oncol. 2001; 19: 3385–91.
10. Curt GA, Breitbart W, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist. 2000; 5: 353-60.
11. Stone P, Richardson A, et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Form. Ann Oncol. 2000; 11: 971-5.
12. Symptom Management in Cancer: Pain, Depression, and Fatigue. NIH State-of-science statements. 2002, Jul 15-17;19; 1-29.
13. Lawrence DP, Kupelnick B, et al. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. J Natl Cancer Inst Monogr. 2004; 32: 40-50.
14. Lee BN, Dantzer R, et al. A Cytokine-based neuroimmunologic mechanism of cancer-related symptom. Neuroimmnomodulation 2004; 11: 279-92.
15. Cleeland C, Bennett G, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. Cancer 2003; 97: 2919-25.
16. Respini D, Jacobsen PB, Thors C, Tralongo P, Balducci L. The prevalence and correlates of fatigue in older cancer patients. Crit Rev Oncol Hematol. 2003; 47:273-79.
17. Fishbain DA, Cole B, Cutler RB, Lewis J, Rosomoff HL, Rosomoff R. Is pain fatiguing? Pain Med. 2003; 4: 51-62.
18. Coats AJ. Origin of symptoms in patients with cachexia with special reference to weakness and shortness of breath. Int J Cardiol. 2002; 85:133-139.
19. Lawlor PG. The panorama of opioid-related cognitive dysfunction in patients with cancer. Cancer. 2002; 94:1836-53.
20. Roscoe JA, Kaufman ME, Matteson-Rusby SE, et al. Cancer-related fatigue and sleep disorders. Oncologist. 2007;12 Suppl 1:35-42.
21. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. Cancer. 2005; 104: 788-93.
22. Ahlberg K, Ekman T, et al. Assessment and management of cancer-related fatigue in adults. Lancet. 2003; 362: 640-50.
23. Seruga B, Zhang H, Bernstein LJ, et al. Cytokines and their relationship to the symptoms and outcome of cancer. Nat Rev Cancer. 2008 Nov;8(11):887-99.
24. Klepser TB, Klepser ME. Unsafe and potentially safe herbal therapies.Am J Health Syst Pharm. 1999 Jan 15;56(2):125-38.Sticher O. Getting to the root of ginseng. Chemtech 1998; 28: 26-32.
25. Attele AS, Wu JA, et al. Ginseng pharmacology: multiple constituents and multiple actions. Biochem Pharmacol. 1999; 58:1685-93.
26. Kim JH, Park CY, et al. Effects of ginseng on subjective quality of life in cancer patients: a double-blind, placebo-controlled pilot trial. J Clin Pharm Ther. 2006; 31: 331-4.
27. Van Kampen J, Robertson H, et al. Neuroprotective actions of the ginseng extract G115 in two rodent models of Parkinson's disease. Exp Neurol. 2003;184: 21–29.
28. Vogler BK, Pittler MH, et al. The efficacy of ginseng. A systematic review of randomised clinical trials. Eur J Clin Pharmacol. 1999; 55: 567–75
29. Barton DL, Soori GS, et al. A pilot, multi-dose placebo-controlled evaluation of American ginseng (*Panax quinquefollius*) to improve cancer-related fatigue: NCCTG trial NO3CA. Am. J. Clin. Oncol. 2007; 25: Abstract 9001.
30. Lenz E, Pugh L, et al. The middle-range theory of unpleasant symptoms: an update. Adv Nur Sci. 19;14-27: 1997.
31. Serum levels of IL-6 and TNF-α correlate with clinicopathological features and patient survival in patients with prostate cancer. Br J Cancer. 90: 2312-16.
32. Adler HL, McCurdy MA, et al. Elevated levels of circulating interleukin-6 and transforming growth factor-β1 in patients with metastatic prostatic carcinoma. J Urol. 1999; 161: 182-7.
33. Gupta S, Aggarwal S, et al. Cytokine production by adherent and non-adherent mononuclear cells in chronic fatigue syndrome. J Psychiat Res. 1997; 31:149-56.

34. Cheney PR, Dorman SE, et al. Letters and corrections: interleukins-2 and the chronic fatigue syndrome. Ann. Intern. Med. 1989; 110: 321.
35. Schubert C, Hong S, Natarajan L, et al., The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review, Brain Behav Immun **21** (2007), pp. 413–427.
36. Exacerbated fatigue and motor deficits in interleukin-10-deficient mice after peripheral immune stimulation. Am J Physiol Regul Integr Comp Physiol. 2008 Oct;295(4):R1109-14.
37. Konsman JP, Parnet P, et al. Cytokine-induced sickness behavior: mechanisms and implications.Trends Neurosci. 2002; 25:154-9.
38. Dantzer R.Cytokine-induced sickness behavior: where do we stand? Brain Behav Immun. 2001;15: 7-24.
39. Bluthe RM, Michaud B, et al. Role of IL-6 in cytokine-induced sickness behavior: a study with IL-6 deficient mice. Physiol Behav. 2000; 70: 367-73.
40. Payne J. Biomarkers, fatigue, sleep and depressive symptoms in women with breast cancer: a pilot study. Oncol Nurs Forum 2006; 33: 775-83.
41. Yennurajalingam S, Bruera E. Palliative Management of Fatigue at the Close of Life: "It Feels Like My Body Is Just Worn Out" JAMA. 2007;297:295-304.
42. Oldervoll LM, Loge JH, Paltiel H, et al. The effect of a physical exercise program in palliative care: a phase II study. J Pain Symptom Manage. 2006; 31: 421-30
43. The review of natural products. St. Louis: Facts and Comparisons; 1997.
44. Dharmananda S. The nature of ginseng. Traditional use, modern research, and the question of dosage. HerbalGram. 2002; 54: 34-51.
45. Kennedy DO, Scholey AB. Ginseng: potential for the enhancement of cognitive performance and mood. Pharmacol Biochem Behav 2003; 75: 687-700.
46. Reay JL, Kennedy DO, et al. Effects of *Panax ginseng*, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks. J Psychopharmacol. 2006; 6:771-81.
47. Sugaya A, Yuzurihara M, et al. Proliferative effect of ginseng saponin on neurite extension of primary cultured neurons of the rat cerebral cortex. J Ethnopharmacol. 1988; 22: 173-81.
48. Liao B, Newmark H, et al. Neuroprotective effects of ginseng total saponin and ginsenosides Rb1 and Rg1 on spinal cord neurons in vitro. Exp Neurol. 2002; 173: 224-34.
49. Braughler JM, Chase RL, et al. A new 21-aminosteroid antioxidant lacking glucocorticoid activity stimulates adrenocorticotropin secretion and blocks arachidonic acid release from mouse pituitary tumor (AtT-20) cells. J Pharmacol Exp Ther. 1988; 244: 423-27.
50. Chu GX, Chen X. Anti-lipid peroxidation and protection of ginsenosides against cerebral ischemia-reperfusion injuries in rats. Zhongguo Yao Li Xue Bao. 1990; 11: 119-23.
51. Chang MS, Lee SG, et al. Transcriptional activation of Cu/Zn superoxide dismutase and catalase genes by panaxadiol ginsenosides extracted from *Panax ginseng*. Phytother Res. 1999; 13: 641-4.
52. Kim S, Rhim H. Ginsenosides inhibit NMDA receptor-mediated epileptic discharges in cultured hippocampal neurons. Arch Pharm Res. 2004; 27: 524-30.
53. Kim S, Ahn K, et al. Inhibitory effect of ginsenosides on NMDA receptor-mediated signals in rat hippocampal neurons. Biochem Biophys Res Commun. 2002; 296: 247-54.
54. Seong YH, Shin CS, et al. Inhibitory effect of ginseng total saponins on glutamate-induced swelling of cultured astrocytes. Biol Pharm Bull. 1995; 18: 1776-8.
55. Gong YS, Zhang JT. Effect of 17-beta-estradiol and ginsenoside Rg1 on reactive microglia induced by beta-amyloid peptides. J Asian Nat Prod Res. 1999; 1:153-61.
56. Benishin CG. Actions of ginsenoside Rb1 on choline uptake in central cholinergic nerve endings. Neurochem Int. 1992; 21: 1–5.
57. Zhang JT, Qu ZW, et al. Preliminary study on antiamnestic mechanism of ginsenosides Rb1 and Rg1. Chin Med J. 1990; 103: 932-8.

58. Itoh T, Zang YF, et al. Effects of *Panax ginseng* root on the vertical and horizontal motor activities and on brain monoamine-related substances in mice. Planta Med. 1989; 55: 429-33.
59. D'Angelo L, Grimaldi R, et al. A double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers. J Ethnopharmacol. 1986; 16:15-22.
60. Petkov V. Effect of ginseng on the brain biogenic monoamines and 3', 5'-AMP system. Experiments on rats. Arzneimittelforschung. 1978; 28: 388-93.
61. Kurimoto H, Nishijo H, et al. Effects of nonsaponin fraction of red ginseng on learning deficits in aged rats. Physiol Behav. 2004; 82: 345-55.
62. Sorensen H, Sonne J. A double-masked study of the effect of ginseng on memory functions. Curr Ther Res. 1996; 57: 959-68.
63. Kim YR, Lee SY, et al. *Panax ginseng* blocks morphine-induced thymic apoptosis by lowering plasma corticosterone level. Gen Pharmacol. 1999; 32: 647-52.
64. Nemmani KV, Ramarao P. et al. Ginsenoside Rf potentiates U-50, 488H-induced analgesia and inhibits tolerance to its analgesia in mice. Life Sci. 2003; 72: 759-68.
65. Kim S., Ahn K., et al. Inhibitory effect of ginsenosides on NMDA receptor-mediated signals in rat hippocampal neurons. Biochem. Biophys. Res. Commun. 2002; 296:247-54.
66. Smolinski AT, Pestka JJ. Modulation of lipopolysaccharide-induced proinflammatory cytokine production in vitro and in vivo by the herbal constituents apigenin (chamomile), ginsenoside Rb(1) (ginseng) and parthenolide (feverfew). Food Chem Toxicol. 2003; 41:1381-90.
67. Cho JY, Yoo ES, et al. In vitro inhibitory effect of protopanaxadiol ginsenosides on tumor necrosis factor (TNF)-alpha production and its modulation by known TNF-alpha antagonists. Planta Med. 2001; 67: 213-8.
68. Yu SC, Li XY. Effect of ginsenoside on IL-1β and IL-6 mRNA expression in hippocampal neurons in chronic inflammation model of aged rats. Acta Pharmacol Sin. 2000; 21: 915-8.
69. Hofseth LJ, Wargovich MJ. Inflammation, cancer, and targets of ginseng. J Nutr. 2007;137:183S-185S.
70. Pannacci M, Lucini V, et al. *Panax ginseng* C.A. Mayer G115 modulates pro-inflammatory cytokine production in mice throughout the increase of macrophage toll-like receptor 4 expression during physical stress. Brain Behav Immun. 2006; 20: 546-51.
71. Le Gal M, le Cathebras P. et al. Pharmaton capsules in the treatment of functional fatigue: a double-blind study versus placebo evaluated by a new methodology. Phytother Res. 1996; 10: 49-53.
72. Younus J, Collins A, et al. Proc Am Soc Clin Oncol. 22: 2003.
73. Engels HJ, Said JM, et al. Failure of chronic ginseng supplementation to affect work performance and energy metabolism in healthy adult females. Nutr Res. 1996; 16: 1295-1305.
74. Teves MA, Wright JE, et. al. Effects of ginseng on repeated bouts of exhaustive exercise. Med Sci Sports Exerc. 1983;15:162.
75. Allen JD, McLung J, et al. Ginseng supplementation does not enhance healthy young adults' peak aerobic exercise performance.J Am Coll Nutr. 1998;17: 462-6.
76. Engels, HJ, Kolokouri I, et al. Effects of ginseng supplementation on supramaximal exercise performance and short-term recovery. J Strength Cond Res. 2001;15: 290-295.
77. Engels HJ, Wirth JC. No ergogenic effects of ginseng (*Panax ginseng* C.A. Meyer) during graded maximal aerobic exercise. J Am Diet Assoc. 1997; 97:1110-5.
78. Sharma AK, Agrawal A, et al. Influence of Mentat (BR-16A) on memory and mental fatigue in cases of anxiety neurosis and depression. Ind J Cancer Res. 1990; 3: 27.
79. Montgomery SA, Thal LJ, et al. Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. Int Clin Psychopharmacol. 2003; 18: 61-71.
80. Wei XY, Yang JY, et al. Anxiolytic effect of saponins from *Panax quinquefolium* in mice. J Ethnopharmacol. 2007; 111: 613-8.

81. Carr N, Bekku N, et al. Identification of anxiolytic ingredients in ginseng root using the elevated plus-maze test in mice, Eur. J. Pharmacol. 2006; 531; 160-5.
82. Cha HY, Park JH, et al. Anxiolytic-like effects of ginsenosides on the elevated plus-maze model in mice, Biol Pharm Bull. 2005; 28: 1621-5.
83. Tode T, Kikuchi Y, et al. Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. Int J Gynaecol Obstet. 1999; 67:169-74.
84. Hsu CC, Ho MC, et al. American ginseng supplementation attenuates creatine kinase level induced by sub maximal exercise in human beings. World J Gastroenterol. 2005; 11: 5327-31.
85. McNaughton LG, Egan G, et al. A comparison of Chinese and Russian ginseng as ergogenic aids to improve various facets of physical fitness. Int J Clin Nutr Rev. 1989; 9: 32-35.
86. Engles HJ, Wirth JC. No ergogenic effects of ginseng (*Panax ginseng*) during graded maximal aerobic exercise. J Am Diet Assoc. 1997; 97: 1110-5.
87. Sharma AK, Agrawal A, et al. Influence of Mentat (BR-16A) on memory and mental fatigue in cases of anxiety neurosis and depression. Ind J Cancer Res. 1990; 3: 27.
88. Darbinyan V, Kteyan A, et al. *Rhodiola rosea* in stress induced fatigue--a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. Phytomedicine. 2000; 7: 365-71.
89. Spasov AA, Wikman GK, et al. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. Phytomedicine. 2000; 7: 85-9.
90. Kim JH, Park CY, et al. Effects of Sun Ginseng on subjective quality of life in cancer patients: a double-blind, placebo-controlled pilot trial. J Clin Pharm Ther. 2006; 31: 331-4.
91. NCCAM Interim Policy: Biologically Active Agents Used in Complementary and Alternative Medicine (CAM) and Placebo Materials. grants.nih.gov/grants/guide/notice-files/NOT-AT-05-003.html
92. de Andrade E, de Mesquita AA, et al. Study of the efficacy of Korean red ginseng in the treatment of erectile dysfunction. Asian J Androl. 2007; 9: 241-4.
93. Hong B, Ji YH, et al. A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: a preliminary report. J Urol. 2002; 168: 2070-3.
94. Ellis JM, Reddy P. Effects of *Panax ginseng* on quality of life. Ann Pharmacother. 2002; 36:375-9.
95. Han KH, Choe SC, et al. Effect of red ginseng on blood pressure in patients with essential hypertension and white coat hypertension. Am J Chin Med. 1998; 26: 199-209.
96. Kennedy DO, Scholey AB, et al. Differential, dose dependent changes in cognitive performance following acute administration of a *Ginkgo biloba*/*Panax ginseng* combination to healthy young volunteers. Nutr Neurosci. 2001; 4: 399-412.
97. Reay JL, Kennedy DO, et al. Single doses of *Panax ginseng* (G115) reduce blood glucose levels and improve cognitive performance during sustained mental activity. J Psychopharmacol. 2005; 19:357-65.
98. Sievenpiper JL, Sung MK, et al. Korean red ginseng rootlets decrease acute postprandial glycemia: results from sequential preparation- and dose-finding studies.J Am Coll Nutr. 2006; 25:100-7.
99. Gross D, Shenkman Z, et al. Ginseng improves pulmonary functions and exercise capacity in patients with COPD. Monaldi Arch Chest Dis. 2002; 57: 242-6.
100. Caron MF, Hotsko AL, et al. Electrocardiographic and hemodynamic effects of *Panax ginseng*. Ann Pharmacother. 2002; 36: 758-63.
101. Scaglione F, Cattaneo G, et al. Efficacy and safety of the standardised Ginseng extract G115 for potentiating vaccination against the influenza syndrome and protection against the common cold [corrected] Drugs Exp Clin Res. 1996; 22: 65-72.
102. Scaglione F, Ferrara F, et al. Immunomodulatory effects of two extracts of *Panax ginseng* C.A. Meyer. Drugs Exp Clin Res. 1990;16: 537-42.

103. Institute for Nutraceutical Advancement Panax and American Ginseng Assay by HPLC INA Method 103.000.
104. Court WA, Hendel JG, et al. Reversed-phase High-performance Liquid Chromatographic Determination of Ginsenosides of *Panax quinquefolium*. J. Chromatogr A. 1996; 755: 11-7.
105. Fuzzati N, Gabetta B, et al. Liquid chromatography - electrospray mass spectrometric identification of ginsenosides in *Panax ginseng* roots. J. Chromatogr A. 1999; 854: 69-79.
106. Lau AJ, Seo BH, et al. High-performance liquid chromatographic method with quantitative comparisons of whole chromatograms of raw and steamed *Panax notoginseng*. J. Chromatogr A. 2004; 1057: 141-9.
107. Jaksch F, Wang M, et al. Handbook of Analytical Methods for Dietary Supplements. 2005, Washington, DC: American Pharmacists Association. 215.
108. Hall T, et al., Evaluation of consistency of standardized asian ginseng products in the ginseng evaluation program. HerbalGram. 2001; 52: 31-45.
109. Coon JT, Ernst E. *Panax ginseng*: a systematic review of adverse effects and drug interactions. Drug Saf. 2002; 25: 323-44.
110. Stavro PM, Woo M, et al. Long-term intake of North American ginseng has no effect on 24-hour blood pressure and renal function. Hypertension. 2006; 47: 791-6.
111. Siegel RK. Ginseng abuse syndrome. Problems with the panacea. JAMA . 1979; 241: 1614-5.
112. Tyler VE. Herbs of Choice: The Therapeutic Use of Phytomedicinals. New York, NY: Pharmaceutical Products Press; 1994.
113. Schulz V, Hansel R, Tyler VE. Rational Phytotherapy: A Physicians' Guide to Herbal Medicine. 3rd ed. Berlin: Springer-Verlag; 1998.
114. Yuan CS, Wei G, et al. American ginseng reduces warfarin's effect in healthy patients. Ann Intern Med . 2004; 141: 23-7.
115. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Health Syst Pharm. 1997; 54: 692-3.
116. Yun TK, Choi SY. Non-organ specific cancer prevention of ginseng: a prospective study in Korea. Int J Epidemiol. 1998; 27: 359-64.
117. Ernst E. The risk-benefit profile of commonly used herbal therapies: ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava [published erratum appears in Ann Intern Med 2003;138:79]. Ann Intern Med. 2002; 136: 42-53.
118. Zava DT, Dollbaum CM, et al. Estrogen and progestin bioactivity of foods, herbs, and spices. Proc Soc Exp Biol Med. 1998; 217: 369-78.
119. Amato P, Christophe S, et al. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. Menopause. 2002; 9:145-150.
120. Chan LY, Chiu PY, Lau TK. An in-vitro study of ginsenoside Rb(1)-induced teratogenicity using a whole rat embryo culture model. Hum Reprod . 2003;18: 2166-8.
121. Baldwin CA, Anderson LA, Phillipson JD. What pharmacists should know about ginseng. Pharm J. 1986; 237: 583-6.
122. Hess FG, Parent RA, Cox GE, et al. Reproduction study in rats on ginseng extract G115. Food Chem Toxicol. 1982; 20:189-92.
123. Newall C, Anderson LA, Phillipson JD. Herbal Medicines: A Guide for Health-Care Professionals. London: Pharmaceutical Press; 1996:143,148.
124. Sonnenborn U, Proppert Y. Ginseng (*Panax ginseng* C.A. Meyer). Br J Phytother. 1991; 2: 3-14.
125. Heo JH, Lee ST, Chu K, Oh MJ, Park HJ, Shim JY, Kim M. An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease.Eur J Neurol. 2008 Aug;15(8):865-8.
126. Lee ST, Chu K, Sim JY, Heo JH, Kim M. Panax ginseng enhances cognitive performance in Alzheimer disease. Alzheimer Dis Assoc Disord. 2008 Jul-Sep;22(3):222-6.
127. Oh KJ, Chae MJ, Lee HS, Hong HD, Park K. Effects of Korean red ginseng on sexual arousal in menopausal women: placebo-controlled, double-blind crossover clinical study.J Sex Med. 2010 Apr;7(4 Pt 1):1469-77. Epub 2010 Feb 5.

128. Bruera E, Belzile M, et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. J Clin Oncol. 1998; 16: 3222-9.
129. Bruera E, Roca E, Cedaro L, et al. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep. 1985; 69: 751-4.
130. Bruera E, Fainsinger R, et al. The use of methylphenidate in patients with incident cancer pain receiving regular opiates. A preliminary report. Pain. 1992; 50: 75-7.
131. Bruera E, Driver L, Barnes EA, et al. Patient-controlled methylphenidate for the management of fatigue in patients with advanced cancer: a preliminary report. J Clin Oncol. 2003; 21: 4439-43.
132. Bruera E, Strasser F, et al. The effect of donepezil on sedation and other symptoms in patients receiving opioids for cancer pain: a pilot study. J Pain Symptom Manage. 2003; 26: 1049-54.
133. Bruera E, Miller MJ, Macmillan K, et al. Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain. Pain. 1992; 48:163-6.
134. Bruera E, Ernst S, et al. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. Can Prev Contr. 1998; 2: 74-8.
135. Bruera E, Strasser F, Palmer JL, et al. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. J Clin Oncol. 2003; 21:129-34.
136. Bruera E, Neumann C, et al. Thalidomide in patients with cachexia due to terminal cancer. Preliminary report. Ann Oncol. 1999; 10: 857-9.
137. Yennurajalingam S, Zhang T, Bruera E. The impact of the palliative care mobile team on symptom assessment and medication profiles in patients admitted to a comprehensive cancer center..Support Care Cancer. 2007;15:471-5.
138. Bruera E, Kuehn N, et al. The Edmonton symptom assessment system (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care. 1991; 7: 6-9.
139. Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. Cancer 2000; 88: 2164-71.
140. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue. J Clin Oncol. 2006; 24: 2073-8.
141. Bruera E, El Osta B, Valero V, et al. Donepezil for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol. 2007; 25: 3475-81.
142. Richardson MA, Sanders T**,** Palmer JL, et al. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. J Clin Oncol. 2000 Jul;18(13):2505-14.
143. Jatoi A, Rowland K, Loprinzi CL, et al. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. J Clin Oncol. 2004; 22: 2469-76.
144. Gogos CA, Ginopoulos P, Salsa B, Apostolidou E, Zoumbos NC, Kalfarentzos F. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy. Cancer. 1998; 82: 395-402.
145. Fearon KCH, von Meyendfeldt MF, Moses AGW, et al. Effect of a protein and energy dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. Gut. 2003; 52:1479-86.
146. Zuijdgeest-van Leeuwen SD, Dagnelie PC, et al. Eicosapentaenoic acid ethyl ester supplementation in cachectic cancer patients and healthy subjects: effects on lipolysis and lipid oxidation. Clin. Nutr. 2000; 19: 417-23.
147. Dewey A, Baughan C, Dean T, Higgins B, Johnson I. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. Cochrane Database. Syst Rev. 2007; 24: CD004597.

148. Cella D. Manual of the Functional Assessment of Chronic illness Therapy (FACIT) Measurement System. Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University. Version 4, 1997.
149. Minton O, Richardson. A, Sharpe M, Hotopf M, and Stone P. A Systematic Review and Meta-Analysis of the Pharmacological Treatment of Cancer-Related Fatigue J Natl Cancer Inst, August 20, 2008; 100(16): 1155 - 1166.
150. Johnston M, Pollard B, Hennessey P. Construct validation of the hospital anxiety and depression scale with clinical populations. J Psychosomatic Res. 2000; 48:579-584.
151. American Thoracic Society. ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med. 2002; 166: 111-7.
152. Bruera E, Sweeney C, Willey J, et al. A randomized controlled trial of supplemental oxygen versus air in cancer patients with dyspnea. Palliat Med. 2003; 17: 659-63.
153. Ancoli-Israel S. The role of actigraphy in the study of sleep and circadian rhythms. Sleep. 2003; 26: 342-92.
154. Littner, M. Practice parameters for the use of actigraphy in sleep and circadian rhythms: an update for 2002. Sleep. 2003; 26: 337-41.
155. Reuben, J.M., Lee, B.-N., Johnson, H., et al. Restoration of Th1 cytokine synthesis by T cells of patients with chronic myelogenous leukemia in cytogenetic and hematologic remission with interferon-α. Clin Cancer Res. 2000; 6: 1671-7.
156. Angelova N, Kong H-W, et al. Recent methodology in the phytochemical analysis of ginseng. Phytochem Anal. 2007; 19: 2-16.
157. Segal RJ, Reid RD, Courneya KS, et al.Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer.J Clin Oncol. 2009 Jan 20;27(3):344-51.
158. Segal RJ, Reid RD, Courneya KS, et al.Resistance exercise in men receiving androgen deprivation therapy for prostate cancer.J Clin Oncol. 2003 May 1;21(9):1653-9.
159. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE: Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage 2002;24:547–561.
160. Thall PF, Simon RM, Estey EH. New Statistical Strategy for Monitoring Safety and Efficacy in Single-Arm Clinical Trials J Clinical Oncology 14(1), 1996, pp296-303.
161. Cella DF, Tulsky DS, Gray G, et al: The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of Clinical Oncology 11:570-9, 1993