Supplementary Table S1. Differences in Baseline Patient Characteristics between Patients that were Randomized and Completed (N=63), and not Completed the Study Interventions (n=29).

Patient Characteristics		**Completed the Study intervention**		
		No (n=29)	Yes (n=63)	P*
Age (median, IQR)		56 (45.5, 65.5)	59 (50, 69)	0.65
FACIT F (median, IQR)		35 (25, 46.5)	27 (22, 34)	0.29
FACT G (median, IQR)		85.5 (84.25, 93.5)	75.5 (62.50, 86.71)	0.12
Cancer Type (n, %)	Breast	9 (31)	18 (28.6)	0.08
	Digestive/Gastrointestinal	10 (34.5)	27 (42.9)	
	Endocrine and Neuroendocrine	0	3 (4.8)	
	Genitourinary	0	6 (9.5)	
	Gynecological	1 (3.4)	3 (4.8)	
	Respiratory/Thoracic	5 (17.2)	5 (7.9)	
Gender (n, %)	Female	20 (69)	40 (63.5)	0.39
Race (n, %)	Asian	1 (3.4)	1 (1.6)	0.17
	African American	6 (20.7)	7 (11.1)	
	Unknown	5 (17.2)	5 (7.9)	
	White or Caucasian	17 (58.6)	50 (79.4)	
Ethnicity (n, %)	Hispanic or Latino	8 (27.6)	11 (17.5)	0.12
Cancer treatment (n, %)	Chemotherapy	23 (79)	38 (60.3)	0.10
	Radiation therapy	6 (20.7)	14 (22)	1
	Targeted therapy	10 (34.4)	27 (42.9)	0.62

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-G, Functional Assessment of Cancer Therapy-General; IQR, interquartile.

*P value calculated using chi-square or Wilcoxon rank sum test

Appendix 1: A Combination Therapy for Cancer-Related Fatigue in Advanced Cancer Patients

A. OBJECTIVES

Cancer-related fatigue (CRF) is the most frequently reported symptom associated with cancer and its treatment. CRF is more severe and debilitating in patients with advanced cancer than in those with early cancer or in cancer survivors[1-4]. Its frequency ranges from 60% to 90% in patients who are receiving palliative care[4,5]. As a result of improved therapy, patients with advanced cancer are living longer, and due to advances in treatment for pain and nausea, clinicians are more frequently recognizing CRF as an important symptom that negatively affects quality of life (QOL), interferes with daily activity, has potentially devastating social and economic consequences, and affects the patient's ability to receive palliative cancer therapy[6]. However, only a few studies have been conducted to determine whether established therapies for CRF such as physical activity are effective in palliative care patients[3,5,7]. In addition, prior pharmacological studies for CRF in palliative care have shown mixed results[1,7,8]. Given the high frequency and adverse effects of CRF and the limited treatment options in advanced cancer patients, further research on new treatment strategies is greatly needed.

Preliminary data from our group[9] and others[7,9-14] have shown that corticosteroids are able to improve CRF and related symptoms in patients with advanced cancer. A recent randomized double blind placebo controlled study[15] by our team was the first to demonstrate that dexamethasone (DEX) use is safe and results in significant improvement in CRF using validated tools. Previous preliminary studies with less validated instruments had similar results[9,14]. However only 33% of patients given DEX at 4 mg/day twice a day showed clinically relevant improvement in CRF or robust response (defined as ≥10 points on the Functional Assessment of Cancer Illness Therapy-Fatigue (FACIT-F) subscale)[16]. Recent results have indicated that DEX at 8 mg/day for one week is safe and shows improvement over the minimal clinically important difference[15], but these results leave room for further reduction of CRF. Physical activity (PA) has the best evidence for treatment of CRF but its own effect size is modest (0.23) in improving CRF[17]. Hence, a combination of PA and a short course of DEX could potentially provide clinically relevant improvement due to its anti-inflammatory effect and improvements in symptom distress and overall well-being. Additionally, DEX would facilitate initiation and adherence to the PA intervention, and thereby engage and sustain PA over the 4 week study period due to its prompt actions based on the results of the recent study by our team[15]. Our **long-term goal** is to reduce CRF and thereby improve QOL in patients with advanced cancer. The **objective** of the proposed study is to build on our prior studies to evaluate the feasibility and preliminary efficacy of the combination of physical activity and a short course of dexamethasone (hereafter abbreviated PA+ DEX) for cancer-related fatigue in advanced cancer. Thus, **our over-arching hypothesis is that in patients with advanced cancer, the combination of dexamethasone with exercise will prove both feasible and beneficial.** To test this hypothesis, we propose the following Specific Objectives:

Primary Objective 1: To test the hypotheses that patients with CRF will be satisfied with the PA+ DEX intervention, have adequate rates of adherence, and that PA+ DEX will be feasible for patients with CRF.

Sub-Objective 1.1. To determine if the combination of PA+ DEX is a feasible intervention for advanced cancer patients, as evidenced by an adherence rate to daily use of PA+ DEX greater than or equal to 75%.

Sub-Objective 1.2. To determine if patients are satisfied with PA+ DEX, based on more than 75% of patients indicating their satisfaction with PA+ DEX with a rating of "somewhat satisfied" or "completely satisfied."

Secondary Objectives:

Exploratory Objective 2. To test the hypothesis that PA+ DEX (PA for 4 weeks plus dexamethasone 4 mg twice a day for 1 week) will be more efficacious than PA+ placebo (PA for 4 weeks plus placebo for 1 week) on CRF as measured by FACIT-F.

Sub-Objective 2.1. To determine if PA+ DEX results in robust increase in FACIT-F subscale scores (defined as ≥10 point improvement in 60% of patients). Completion of Objectives 1 and 2 will inform our design of an adequately powered, R01-funded study of PA+ DEX.

Exploratory Objective 3. To explore the effects of PA+ DEX on fatigue-related symptoms and function.

Sub-Objective 3.1. To determine if PA+ DEX improves CRF by targeting the various associated factors of CRF. We will consider both objective and subjective measures, including: inflammation (C-reactive protein as a surrogate marker of inflammation); physical activity and muscle function before and after treatment; and

patient reported outcomes, such as affective/emotional (including depression and anxiety), physical/behavioral (including fatigue and sleep quality), pain, and anorexia. This Sub-Objective will be highly hypothesis-generating.

Summary: We have previously established the safety and feasibility of both DEX and PA, separately, for CRF in patients with advanced cancer. However, the work proposed here is needed to generate data that will allow us to assess the feasibility of the combined, potentially synergistic PA+ DEX intervention, explore new targets for further research, and inform the effect size needed to design an R01 study.

B. BACKGROUND AND SIGNIFICANCE:

Cancer-related fatigue (CRF) is the most frequently reported symptom associated with cancer and its treatment, occurring in 60% to 90% of patients who are receiving palliative care.[4,5] CRF is more severe and debilitating in patients with advanced cancer than in those with early cancer or in cancer survivors.[1-4] As a result of improved therapy, patients with advanced cancer are living longer, and due to advances in treatment for pain and nausea, clinicians are more frequently recognizing CRF as an important symptom that negatively affects quality of life (QOL), interferes with daily activity, has potentially devastating social and economic consequences, and affects the patient's ability to receive palliative cancer therapy.[6] However, only a few studies have been conducted to determine whether established therapies for CRF such as physical activity (PA) are effective in palliative care patients.[3,7,8] In addition, prior pharmacological studies for CRF in palliative care have shown mixed results.[1,7,9] Given the high frequency and adverse effects of CRF and the limited treatment options in advanced cancer patients, further research on new treatment strategies is greatly needed.

Rationale: In a prior study, dexamethasone (DEX) 4 mg orally twice daily was associated with significant improvement of fatigue at Day 8 in DEX arm compared to the placebo arm [8.01 (7.81) vs 3.06 (7.28), p=0.005] and was also found to be safe.[15] However, only 33% of patients given DEX at this dose showed clinically relevant improvement in CRF or a robust response (defined as ≥10 points on the FACIT-F subscale).[16] PA is also beneficial for CRF (Level 1 evidence); however, there are limited studies in patients with advanced cancer.[17] Therefore, the study we describe here provides a unique opportunity to test, for the first time, the combination of a short course of DEX (which would improve CRF in the short term) with PA, with the idea that DEX treatment would allow initiation of and long-term adherence to the PA intervention, which is currently the best-evidenced intervention for CRF. The goal of this project is to show that the DEX+ PA intervention is feasible and would provide more robust improvement of cancer related fatigue than PA alone as the use of DEX would enable the patient to better initiate and adhere to the PA intervention. We also anticipate the study will be safe and feasible based on preliminary data from previous studies in which 341 advanced cancer patients received a similar dose of DEX or its equivalent as will be used in the current study[9] (Tables 1 and 2, below). In addition, we will ensure the safety of the interventions in this patient population through measures such as excluding patients with a history of falls and infections, monitoring blood glucose, and safety monitoring procedures detailed below.

Table 1. Effects of Methylprednisone (MP) on clinical parameters*

	Performance Status (ECOG)	Activity Score	Appetite (visual analogue, 0-100)
Baseline	3.5 ± 0.7	3.2 ± 2	26.5 ± 10
Placebo	3.2 ± 0.6	3.4 ± 2	29.5 ± 15
MP (Days 5-13)	3 ± 0.8	6.7 ± 2.4	40.1 ± 15
MP (Day 33)	3.3 ± 0.8	4 ± 2	33 ± 13
***P* values**			
Baseline vs Placebo	NS	NS	NS
Placebo vs MP (Days 5-13)	NS	<0.01	<0.05
Placebo vs MP (Day 33)	NS	NS	NS

*Unless otherwise specified, values vs mean ± SD. NS: not significant.

Conceptual Model: We adapted the Integrated Fatigue Model (IFM) for this study to explain multidimensional and multifactorial etiology of CRF and its treatments.[18,19] The exact cause and mechanisms of fatigue in patients with advanced cancer remain unknown, although the frequency, severity, and temporal cause of CRF in these patients have been well described.[2,4,5,20] CRF in advanced cancer is likely to occur as a consequence of cancer, its treatment, and patient risk factors, as well as the accompanying inflammation.[1,21-23] Tumor and immune byproducts, along with direct brain effects, are thought to contribute to CRF. In addition to these direct effects of cancer, there are a number of patient-related social and behavioral factors that also contribute to the severity and duration of CRF.[2,21] These factors are summarized in our conceptual model (Figure 1), which shows that the effects of these different factors result in the multidimensional manifestation of CRF (physical, behavioral, sensory, affective, and physiological/biochemical). Our model describes two interventions that can counteract CRF. First, PA uniquely affects health-related fitness outcomes, anxiety, depression, and cognition that have been shown to mediate CRF.[3,24] Second, DEX has direct central nervous system effects, including modulation of the hypothalamic pituitary axis and inflammatory cytokines, action on the reticular activating system (arousal), and effects on mood, which all cause the drug to impact the physical, cognitive, functional, and psychological contributors to CRF.[5] Therapies combining PA with DEX have the potential to improve CRF individually, but they may also demonstrate improvement of CRF through their joint (and potentially synergistic) effects. One of the mechanisms by which we hypothesize the joint effect may occur is via prompt improvement of CRF by DEX, which would then allow a more effective initiation of and adherence to the PA intervention, and ultimately facilitate better maintenance of PA over time. Therefore we hypothesize that the combination of PA+ DEX can mitigate CRF over a medium and long term basis in this distressed population.

Table 2. Corticosteroids (dosage and duration) in the management of cancer-related symptoms

Author and Year	Number of Patients	Treatment Duration (Days)	Study Drug*	Equivalent Dexamethasone Daily Dose (mg)	Primary Outcome of the Study
Moertal *et al*., 1974	116	14	DEX	0.75-1.5	Cancer-related symptoms including low apetite, strength, and overall survival
Wilcox *et al*., 1984	41	14	PS	2.25	Poor apetite
Bruera *et al*., 1985**	40	14	MP	6	Combination of pain, tiredness, anorexia and depression
Della Cuna *et al*., 1989**	40	56	MP	23	Quality of life
Popiela *et al*., 1989**	173	56	MP	23	Quality of life
Loprinzi *et al*., 1999**	455	30	DEX	3	Low appetite
Hardy *et al*., 2001	160	22	DEX	12	Anorexia, nausea, low mood, pain and vomiting
Mercadente *et al*., 2011	376	26	DEX, MP	16-Apr	Cancer related symptoms including anorexia, fatigue, dyspnea, headache and drowsiness
Bruera et al., 2004**	51	7	DEX	20	Chronic nausea
Yennurajalingam *et al*., 2013**	84	14	DEX	8	fatigue
Paulsen et al., 2014**	50	7	MP	8	pain

*MP: Methylprednisone; DEX: Dexamethasone; PS: Prednisolone
**Randomized, double blind placebo controlled studies

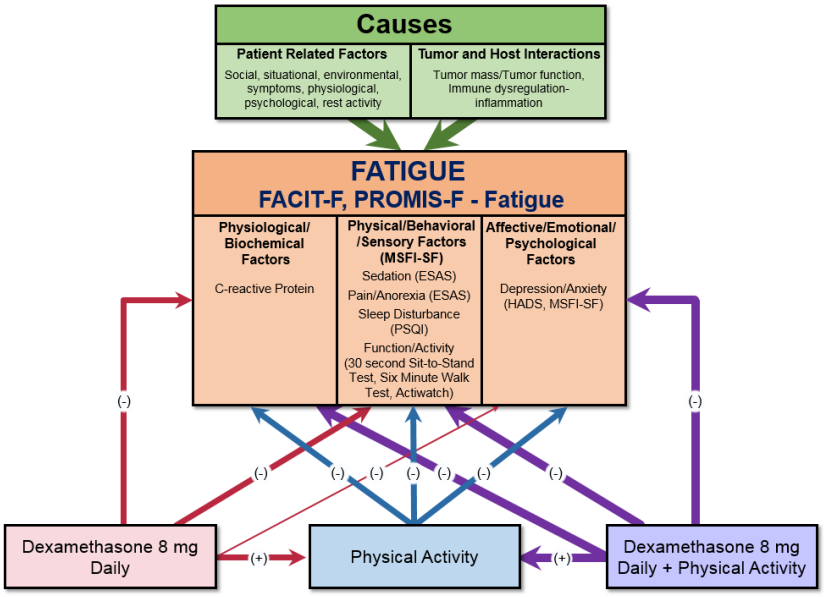
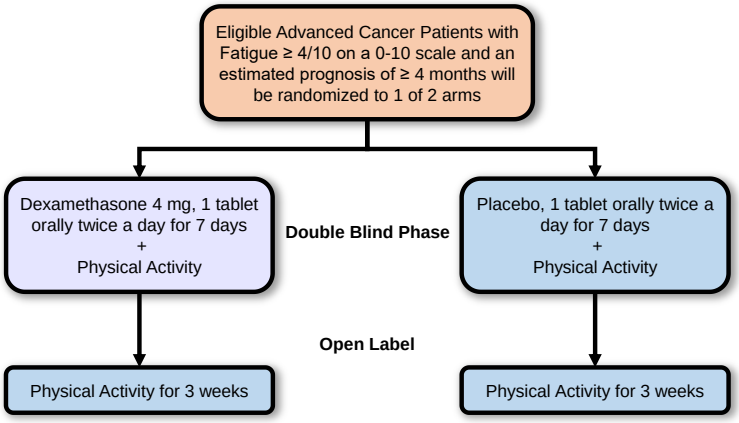


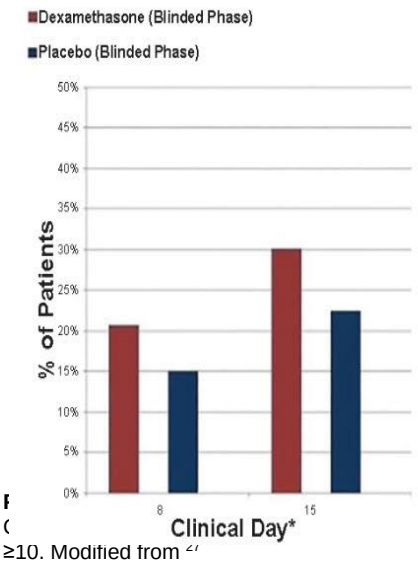
Figure 1. Conceptual model (adapted from the Integrated Fatigue Model) showing various causative factors of multidimensional fatigue and potential targets for study interventions. Thicker lines indicate stronger relationships.

Significance: CRF is severe and debilitating in patients with advanced cancer and its impact on their QOL is a significant medical issue that has yet to be meaningfully impacted by any intervention. Therefore, studies on new strategies are urgently needed. The proposed research is significant because it will be the first to test the effects of the combined interventions of DEX and PA in advanced cancer patients, a group that is living longer as more treatment options are available.[1,6] We anticipate that this combination therapy, if effective, could have the potential to immediately impact the clinical care of advanced cancer patients experiencing fatigue.[9,15,17,25,16] This study will provide important preliminary evidence to demonstrate the joint effects of DEX and PA in improving CRF. Other important benefits of this study are that it will provide important data on the role of the combination intervention in other QOL measures such as anxiety, depression, and the role of combination interventions on objective measures of physical activity, strength, and C-reactive Protein (CRP).

Innovation: Our study is highly innovative in two important ways. First, it will be **the first study to use the combination of a short course of DEX and PA to improve CRF**. Based on our previous work, we hypothesize that the use of DEX will result in a rapid improvement of CRF which will in turn allow the patient to initiate and maintain PA at a level difficult to achieve in the absence of the drug, thereby further mitigating CRF over a medium and long term basis by their joint effects. Second, our study is **the first combination study targeting CRF that will utilize the innovative computer adaptive test for fatigue symptom assessment** that is a part of PROMIS,[26] as well as other validated measures, to capture the factors differentially influencing multidimensional aspects of CRF. These symptom assessment results will constitute an extremely effective hypothesis-generating line of study that will inform our future R01-funded studies and guide our research program in even more highly innovative future directions.



C. PRELIMINARY STUDIES **Pharmacologic Treatment of Fatigue:** Our team's previous studies in patients with advanced cancer have allowed us to establish the high frequency, severity and multidimensional nature of fatigue.[4,9,15,20,25,27-32] We have conducted studies using multiple assessment tools for fatigue and have been able to characterize fatigue in this patient population.[4,20,33-35] In a preliminary study of 31 advanced cancer patients, we found that methylprednisolone (MP) 32 mg/day significantly improved CRF ($p<0.01$) compared with placebo with no significant differences in side-effects between groups.[9] However, as shown in Table 1, this study was unable to detect sustained responses to Day 33. Prior studies conducted in palliative patients by our team and others used various doses of steroids (Table 2). Additionally, in prior studies, in 341 patients who received at least 8 mg /day or equivalent dose of DEX for 7 days there was no report of significant toxicity due to hyperglycemia and myopathy. Significantly, in a recently published[15] RCT study of 84 patients with advanced cancer, oral DEX at 8 mg/day for 14 days was found to be effective in alleviating CRF compared with placebo. The mean improvement in the FACIT-F subscale was significantly higher in the DEX group than in the placebo at Day 8 in DEX arm compared to placebo arm [8.01 (7.81) vs 3.06(7.28), p=0.005] as well as Day 15 (9 [10.3] vs. 3.1 [9.59], P=0.008)[15] (Figure 2) and this is currently the intervention with the best effect size for fatigue in advanced cancer,[36] although it is not strong enough to be considered clinically relevant. Furthermore, the numbers of adverse effects did not significantly differ between the groups at Day 15 (primary end point) and at the end of the open label phase. Based on these preliminary data, we conclude that **8 mg/d of DEX is safe and effective if administered for 7 days**, and therefore propose administration of DEX at 8 mg/day for 7 days in the current study.



≥10. Modified from [27]

Physical activity: In prior studies led by Dr. Basen-Engquist (Co-I), the same PA intervention proposed here was tested in patients with highly symptomatic prostate cancer (TPRB-98-103-01-PBP)[37] and in breast cancer (CA89519)[38] and improved 6-minute walk performance and QOL were observed. In an R01-funded study of physical activity in endometrial cancer survivors,[39] the same PA intervention was completed by a high percentage of subjects and was well received by the participants. An R21-funded study (CA137333) using the same PA intervention in patients similar to those targeted in this proposal found the PA intervention to be safe and feasible, and resulted in improved light and moderate activity and better performance in the 30 second sit-to-stand test. Highly symptomatic prostate patients enrolled in an ongoing study (NCT01410942) conducted by our team (PI: Yennu) and using the same standardized physical activity regimen in combination with a study drug had no difficulty completing all the assessments. Preliminary data suggests 100% (n=51) completed supervised exercise, 98% (49/51) completed all calls, and 74.5% (38/51) met all goals during study period (week 5). In

summary, highly symptomatic patients have been able to complete our proposed PA intervention in multiple previous studies conducted by our group, and thus, we anticipate that the physical activity proposed in the current study would be safe for the targeted study population and could be completed by the majority of our subjects.
D. APPROACH: In this hypothesis-generating feasibility and preliminary efficacy study we will use a randomized double-blind design. Seventy patients will be randomized equally between the 2 treatment arms (Figure 3).

Patient Recruitment: Patients will be recruited from outpatient and supportive care clinics at the MD Anderson Cancer Center and it's Houston Area Locations (HALs). The randomized assignment for the study medication will be obtained via the Department of Biostatistics Clinical Trial Conduct Website Tool. To ensure adequate inclusion of minorities in our studies, all forms will be translated into Spanish, and subjects will be stratified into groups. The PI will obtain approval from the patient's primary oncologist in all cases prior to study enrollment.

Remote consent: Patients may be messaged via MyChart or called over the phone using a verbal script to explain the study. If the patient expresses interest, we will proceed with the screening test which will be administered over video-conference with the patient's verbal consent. The patient study flyer may be sent via MyChart to provide additional details of the study. If the patient is found eligible, they will be sent the consent form through e-mail or mail. Study team will go over the consent form with the patient and the patient will be asked to sign the consent form and return to the study staff either through MyChart, e-mail or pre-addressed stamped envelope. The consent process will be documented in Epic.

Figure 3. Treatment Schema, including PA+ DEX arm (left) and PA+ Placebo Arm (right)

Another recruitment strategy will be to use the EPIC system to identify potentially eligible participants based on key eligibility criteria. Potentially eligible participants will be mailed an IRB approved letter explaining the study opportunity. The letter includes the ability to opt in/opt out regarding receiving further follow up to learn about the study. Potential participants wanting to learn more about the study will be given the information to call the study team directly, or to indicate at the bottom of the letter the best day, time and method to contact them to educate them about the study. A self-addressed, stamped envelope will be included for convenience.

Eligibility Criteria: Our eligibility criteria have been selected to choose subjects able to safely participate in PA and complete the study, including the following **Inclusion Criteria:** Diagnosis of locally advanced cancer (defined as metastatic or recurrent cancer or completed 2 lines of therapy) with fatigue ≥4/10 (0-10 scale) on the Edmonton Symptom Assessment Scale; Presence of fatigue for at least 2 weeks; Normal cognition defined as Memorial Delirium Assessment Scale (MDAS) of </= 13/30 completed in person or via video conference; Hemoglobin >8 g/L within 2 weeks of enrollment in the study; Zubrod performance status ≤ 2; and a life expectancy of ≥4 months, able to read, write, and speak English or Spanish.

To optimize patients' ability to safely complete the study interventions, we will utilize the following **Exclusion Criteria:** Patients with a history of hypersensitivity to dexamethasone or having any contraindication to physical activity as determined by the treating physician; reports of a fall in the past 30 days; uncontrolled diabetes mellitus as defined by a random blood sugar of >200mg/dl not being monitored by their primary care physician; sepsis and/or acute, chronic, or ongoing infections that are currently being treated with systemic antimicrobials**;** current, active peptic ulcer disease; neutropenia as defined by an absolute neutrophil count (ANC) of < 1000 cells/mm; regular participation in moderate- or vigorous-intensity physical activity for ≥30 minutes at least 5 times a week and strength training for ≥2 days; symptomatic cardiac disease (New York Heart Association functional class III or IV) or coronary artery disease; patients currently on immunotherapy; and inability to comply with study protocol procedures.

Rationale for Various Tumor Types: **(1)** CRF is a syndrome that results from increased production of inflammatory cytokines and tumor by-products. This pathophysiology is related more to tumor/host interactions than to any specific histology.[4,20] **(2)** The frequency, severity, and mechanisms of CRF in patients with advanced cancer who have various tumor types are largely the same, on the basis of clinical trials of methylphenidate,[12] donepezil,[9] and fish oil[40] in the treatment of CRF by our group and according to studies by other groups. **(3)** We will obtain a more representative distribution in terms of age, sex, and behavior. **(4)** Independent of cancer type,

those with advanced cancer undergoing treatment for CRF rate CRF as the most significant symptom affecting their QOL. Our ultimate goal is to reduce CRF in this distressed cohort/population.

Treatment Plan: Patients who are eligible and interested in participating will be asked to give written consent and then randomized into 1 of the 2 arms of the study. The length of dexamethasone treatment is seven days. The research nurse/coordinator will conduct all baseline assessments and follow-up as shown in Table 3.

Blinding: The pharmacological treatment assigned to individual patients will be known to only the statistician and investigational pharmacy. Patients, research staff and investigators including the PI conducting the assessment will be blinded to the treatment assignment. Only the pharmacists preparing the study medications and statistician will have access to the treatment assignment. We will maintain allocation concealment. The research nurse will then provide instructions and prescriptions for the study medications (drug or placebo) and will make referrals to trained research nurse/coordinator for exercise intervention.

Table 3. Study Assessments

ASSESSMENTS	Screening	Baseline	Day 3^	Day 8 (±3)^	Day 15 (±3)^	Day 21 (±3)^	Day 29 (±3)^	1 month post study^
History/Physical Exam[§]		X					X	
Zubrod Score		X						
Medication Review		X		X	X	X	X	X
MDAS	X	X**						
ESAS	X	X**		X			X	X
FACIT-F (FACIT-subscale & FACT-G), MFSI-SF, HADS		X**		X			X	X
Godin Leisure-time Physical Activity Questionnaire[#]		X**		X	X		X	X
PSQI		X**			X		X	
PROMIS, Myopathy Questionnaire		X**		X	X		X	X
Physical Performance Tests [~] (30 Second Chair Stand Test and 6 Minute Walk Test)		X		X			X	X[#]
Physical Activity (Pedometer, Actiwatch)		X		X			X	
C-reactive Protein[%]		X[$]					X	
CBC[+],	X							
Blood Glucose+*	X		X*	X*	X*			
Toxicity Evaluation[@]		X	X	X			X	
Satisfaction Scale							X	X
Satisfaction Assessment							X	

***Fasting blood glucose finger sticks on days 3, 8 and 15 at home only**

^ If the patient is unable to return to the clinic, the physical assessments will not be completed and questionnaires will be completed over the phone or video-conference

[+]If the patient has not had blood drawn in the past two weeks, one will be done to determine eligibility

[#]Assessment will be completed by Research Nurse

[@]Adverse effects related to the use of dexamethasone, such as nausea (F, S), pain in the abdomen (F, S, I), vomiting (F, S), hiccups (F, S), shortness of breath (S, I), arm/leg swelling (F, S, I), fatigue (F, I),

insomnia (S, I), sad or unhappy feelings (F,S, I), hives (P), itchy skin (S), and rash (P) will be rated by patients using the PRO-CTCAE.[60-62] F = frequency, S = severity, I = interference with usual or daily activities, P = presence.

% CRP on Day 29 may be conducted within +/- 7 days if patient returns to clinic.

$ CRP for baseline may be conducted with screening labs if CBC is needed for eligibility

**** Assessments may be conducted over the phone or video-conference**
˜ Optional if patient unable to come to the institution.
§ Assessment will be obtained via chart review.

Drug Intervention: Eligible patients will be randomized to receive either a placebo, twice a day for 7 days or 4 mg of dexamethasone, twice a day one capsule in the morning and one capsule in the afternoon prior to 3pm.(timed to prevent insomnia)[15] for 7 days. The matching placebo will be prepared from inactive excipient methylcellulose by an external compounding pharmacy and will have the same color and identical packaging as the 4 mg DEX capsules. All patients will be given a proton pump inhibitor (Pantoprazole 40mg once daily during the course of their treatment. During the study, blood glucose will be monitored and hyperglycemia will be managed at the Supportive Care Center by the PI (Dr. Sriram Yennu MD, MS) under the supervision of our endocrine collaborator (Dr. Busaidy) who will be consulted as necessary. We will collect blood samples at baseline and day 29 and patients will perform fasting finger sticks (after instruction) using the glucometer on day 3 (+/-1), day 8 (+/-1), and day 15 (+/-1) to monitor the blood glucose levels. We will also monitor for myopathy, a potential side effect of DEX, as described below. Evaluation of adherence will be done as part of the weekly medication review by the research coordinator (See Table 3).

Study drug and supplies may be mailed to participants.

Physical Activity (PA) or Exercise Intervention: Briefly, our study will use a standardized PA intervention tailored to patients with advanced cancer and based on American College of Sports Medicine (ACSM) exercise recommendations and prior studies by our team.[41] We will use a combination of supervised sessions, led by a trained research nurse/coordinator, and a home PA regimen including resistance training and moderate intensity walking, timed to prevent exercise-induced inflammation.[42-44] Participants will have at least 2 supervised session during the course of the study. The trained research nurse/coordinator will meet with each participant to evaluate his or her current strength and aerobic fitness level and to teach the assigned exercises. At each supervised session the patient will perform the resistance exercise and moderate intensity walking, depending on the patient's tolerance as assessed by the trained research nurse/coordinator. The resistance exercise sessions are designed so that the individual begins with a lighter resistance and progresses to heavier resistance once a level has been mastered. Likewise, the frequency and duration of the walking program will be established based on the trained research nurse/coordinator's assessment of the participant's baseline aerobic fitness level. Participants will be asked to walk a minimum of 5 days a week at the duration established by the trained research nurse/coordinator. Participants will also receive a weekly coaching call from the trained research nurse/coordinator to assess their progress. Safety will be assessed during these phone calls and discussed with the Principal Investigator (PI) as soon as possible. The frequency, intensity, and duration of the assigned exercises will also be evaluated and adjusted as necessary. To ensure adherence to the exercise protocol, video and audio recordings will be made of in-person and remote sessions and telephone sessions, respectively. Dr. Basen-Engquist will review a selection of the sessions to evaluate the trained research nurse/coordinator's adherence to the protocol. We will use the 30 second chair stand test, six-minute walk test, the Godin leisure-time physical activity questionnaire, pedometer log and exercise diary to complement objective measures such as actiwatch and pedometer (steps/day) to assess the PA prescription and its effects on day time activity as well as adherence. During or after the 6-minute walk test, if a patient desaturates, patient will be referred to the treating physician for management, and would be withdrawn from the study. To objectively measure overall activity level, patients will wear an Actiwatch portable recorder (Mini Mitter Company, Inc. A Respironics, Incs., OR, USA) for 3-5 days prior to treatment and during the duration of the study. The data then will be separated to distinguish it before and after treatment. A Myopathy questionnaire will be administered at baseline, Days 8,

15, 29, and one month after the last visit. The Satisfaction Scale (Appendix L) will be used to assess patient satisfaction on the last day the research coordinator sees the patient and one month after the last visit. Participants will receive a postage paid envelope to return the actiwatch and pedometer for data retrieval.

The participant will be provided up to two $12 parking vouchers for a total of $24 when attending in-person supervised exercise visits.

Study data may be entered directly into Microsoft Access.

Objective 1: To test the hypotheses that patients with CRF will be satisfied with the PA+ DEX intervention, have adequate rates of adherence, and that PA+ DEX will be feasible for patients with CRF. Variables to be evaluated include rates of participant recruitment and retention, frequency of use of the physical activity prescription and percentage of completion by subjects, the proportion of pills taken, acceptability of the physical activity and study drug to patients, and barriers to participation.
Sub-Objective 1.1: In this Sub-Objective, **Two measures of PA adherence will be calculated:** first, as the mean of the percentage of total prescribed strength training sessions; and second, as the percentage of total prescribed walking regimen minutes completed. For these measures, exercise data will be obtained from exercise diaries, in which the participants record their leisure time activities, resistance exercise sessions, time spent in moderate intensity walking, and the number of steps they take each day. The physical activity questionnaire, pedometer logs, and actiwatch data will be used to complement the exercise diaries. **To assess adherence to the medication regime**, the mean (across all patients) percentage of total prescribed study medication pills taken will be calculated, obtained from pill count of time-and-date-stamped returned bottles.
Sub Objective 1.2: In Sub-Objective 1.2, **Satisfaction will be assessed** using a 5 point, fully word-anchored balanced bipolar scale (Satisfaction Assessment). We are confident that we can successfully accrue the necessary number of study patients, based on the prior successful accrual of more than 500 patients in other fatigue treatment trials (NCT01410942) for CRF[45] that had eligibility criteria similar to those in our proposed study.[25,28-31,40]

Potential Pitfalls and Alternative Strategies: Our study population consists of patients who are very active and have been selected based on their likely ability to safely complete the PA intervention (please refer to Eligibility Criteria for details). Therefore, we do not anticipate problems retaining study subjects. However, if such problems occur we will consider adjusting our PA intervention to improve subjects' ability to continue the study.

Objective 2: To test the hypothesis that PA+ DEX (PA for 4 weeks plus dexamethasone 4 mg/day twice a day for 1 week) will be more efficacious than PA+ placebo (PA for 4 weeks plus placebo for 1 week) on CRF as measured by FACIT-F. FACIT-F is a well-validated QOL instrument[46] and was chosen as the primary outcome measure since it has been successfully used in CRF treatment trials by our team and by others.[25,28,29,31,47] The fatigue subscale is a patient-rated assessment of the intensity of fatigue and its related symptoms on a scale of 0 to 4. It has been shown to have strong internal consistency (α = 0.93–0.95), sensitivity of 0.92, and specificity of 0.69.

Potential Pitfalls and Alternative Strategies: Based on our group's previous studies, we do not anticipate difficulties accruing and retaining study subjects. However, even if our recruitment is inadequate or patients are unable to complete the interventions, we will still be able to mine the data we collect for other significant outcomes. Furthermore, these data will inform our further studies of PA+ DEX and allow us to refine our interventions. It is possible that merely initiating increased PA will increase QOL measures.[48]

Exploratory Objective 3. To explore the effects of PA+ DEX on fatigue-related symptoms and functions: In this hypothesis-generating Objective, we will examine individual aspects of CRF to gain high-resolution and potentially mechanistic insight into its modulation by PA+ DEX. Measurements will occur from the beginning of the study until day 60, which will enable us to monitor long-term safety and efficacy, and inform our understanding of the effects of PA+ DEX over time. Our chief tool will be the **Patient Reported Outcome Measurement Information System – Fatigue (PROMIS-F)** instrument, which measures key symptoms and health concepts

applicable to advanced cancer, enabling efficient and interpretable clinical trial research and clinical practice application of patient-reported outcomes (PROs) .[49,50,26] The PROMIS fatigue measure used in the current study was found to be highly correlated with the legacy measures.[26] Additional measures include: 1) **The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF)** consists of 30 items designed to assess the multidimensional nature of fatigue.[51] Ratings are summed to obtain scores for 5 subscales (general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor); 2) **Hospital Anxiety Depression Scale (HADS)** is a 14-item questionnaire has been validated in a number of clinical situations and has been widely used in medically ill patients;[52] 3) the **Pittsburg Sleep Quality Index (PSQI)** instrument provides a brief, clinically useful assessment of a variety of sleep disturbances that might affect sleep quality;[53] **4)** the **30 second sit-to-stand test** will be administered at baseline, Day 8, Day 29, and one month after the last visit so as to assess lower body strength;[51] **5)** the **6 Minute Walk Test (6MWT)** will be used to assess physical function and has been recommended by the American Thoracic Society (ATS) as an objective measure of functional capacity. Per American Thoracic Society (ATS) recommendations, the 6MWT will be performed indoors, along a long, flat, straight, minimally traveled, enclosed corridor with a hard surface, located in the Behavioral Research and Treatment Center at MD Anderson. The walking course will be 30 m in length (marked every 3 m with brightly colored tape) along a hallway that has a 100 ft. clear pathway. A starting line (also marked with brightly colored tape) marks the beginning and end of each 60-m lap. The turnaround points will be marked with a bright orange traffic cone. The six-minute walk test has high test-retest and inter-tester reliability, and its validity is supported by correlations with self-report measures of fatigue and functional status;[54] and 6) **CRP** level, a surrogate marker of inflammation, will be collected at baseline, and Day 29 +/- 7 days.

Potential Pitfalls and Alternative Strategies: A potential concern when introducing patients to a PA regimen is exercise-induced inflammation. However, while an acute and transitory increase in inflammation usually occurs immediately after moderate-to-severe intensity exercise,[55] recent evidence suggests the possibility of a decrease in inflammation in the long term.[42-44] Thus, we do not anticipate that inflammation will increase due to the PA intervention, and may even improve. Furthermore, while we do not anticipate difficulties with this Objective, any failure to collect data from these measurements will be informative and influence our design of future studies.

Table 4. Project Time Line for Grant Activities (Months)

Task	1-2	3-12	13-24
Staffing	→		
Training	→		
Study Initiation	→	→	
Patient enrollment (5-6 patients/month)		→	→
Data Collection		→	→
Data entry and monitoring		→	→
Data analyses			→
Abstract and Manuscript Preparation			→

E. STATISTICAL CONSIDERATIONS: The primary study objective is to assess the feasibility, adherence, and satisfaction with Dexamethasone (DEX) combined with physical activity (PA). Oversight by the PI, weekly research team meetings, continuous training of the research team, and the physical activity and statistical expertise of key personnel will ensure rigorous experimental design and collection of unbiased results. We will perform all analyses on the total population as well as considering potential differences in response between males and females, and take into consideration any other effects that can be investigated with the demographic data we collect. Adherence will be calculated as the mean of the % of total prescribed strength training sessions and the % of total prescribed walking regimen minutes completed (exercise), and mean (across all patients) percentage of total prescribed pills taken (study medication) as detailed above. We will estimate 95% confidence intervals for the proportion of patients completing the intervention, the adherence rate, and the proportion of patients with a satisfaction rating of “somewhat satisfied” or “completely satisfied.” PA+ DEX will be deemed feasible if adherence rate to daily use of *PA+ DEX* during the 4-week intervention is ≥75% and more than 75% of patients will indicate satisfaction with the *PA+ Dex* with a rating of “somewhat satisfied” or “completely satisfied.” Adherence is defined as 75% of pills prescribed; 65% of walking exercise prescribed; and 65% of resistance exercise prescribed. With 35 patients in each arm, a 95% confidence interval for 0.75 would have a half width of 0.15.

Sample Size Justification: Our prior data[16] (Figure 2) showed that 4 mg twice a day of *DEX* resulted in clinically relevant improvement (≥10 points change in the FACIT-F score) in 33% of patients. In the current study, a change in FACIT-F subscale scores will be evaluated in the PA+DEX group (4 mg orally of dexamethasone twice a day

for 7 days) and PA+placebo group; both groups also will also undergo 4 weeks of PA intervention (See Treatment Schema Figure 3). To obtain a reliable estimate of clinically relevant or robust improvement at Day 8, we need 35 subjects in each group with a total sample size of 70. If the robust response proportions are 0.33 or 0.60, the half-widths of 95% confidence intervals will be 0.16. In order to observe 70 patients, we will recruit a total of 100, assuming that 30% of those recruited will either be screen failures or withdraw on or before Day 1 (prior to randomization and prior to treatment). Only those patients who withdraw prior to randomization or study treatment will be replaced. Because this is a feasibility study, patients who withdraw after first study treatment will be considered evaluable for feasibility and therefore not be replaced. To address issues related to missing data, we will perform multiple imputation analyses.[72] We recognize the potential need for steroids while receiving other therapies and will collect the relevant information and include it as covariates in the secondary analysis. Since FACIT-F scores will be obtained at 0, 8, 15, 29, and 60 days, we will also analyze the data by using linear mixed effects longitudinal models. We will perform exploratory data analyses to assess treatment effects for other continuous outcome variables including MFSI-SF, PROMIS, HADS, PSQI scores and measures such as sit and stand, 6MWT, and CRP levels by using the same statistical methods described above. Before performing inferential procedures, we will conduct extensive descriptive statistical analyses of the outcome and predictor variables. Standard descriptive statistics, including means, standard deviations, ranges, and frequencies, will be computed where appropriate. Distributional characteristics of relevant variables will also be closely examined using box plots and histograms. If the data do not appear to be approximately normally distributed, transformations will be made to the data, or appropriate nonparametric methods will be used. We anticipate all analyses will be complete 24 months after study initiation (See Table 4).

Future Studies: Preliminary data obtained from this feasibility and early efficacy study will be used to conduct a larger, well-designed study to determine the effectiveness of PA+ Dex and to test the hypothesis that dexamethasone increases patients' adherence to physical activity (synergistic or joint effects). We will also directly test how PA+ Dex mediates the role of various dimensions of fatigue (Figure 1) and the effects of PA+ Dex on inflammatory cytokine levels. In further studies, we will pursue exciting new lines of investigation uncovered in the hypothesis-generating Objectives of the current study.

REFERENCES

1. Berger AM, Abernethy AP, Atkinson A, et al. Cancer-related fatigue. *J Natl Compr Canc Netw.* 2010;8(8):904-931.

2. de Raaf PJ, de Klerk C, Timman R, Hinz A, van der Rijt CC. Differences in fatigue experiences among patients with advanced cancer, cancer survivors, and the general population. *J Pain Symptom Manage.* 2012;44(6):823-830.

3. Butt Z, Rosenbloom SK, Abernethy AP, et al. Fatigue is the Most Important Symptom for Advanced Cancer Patients Who Have Had Chemotherapy. *Journal of the National Comprehensive Cancer Network.* 2008;6(5):448-455.

4. Yennu S, Urbauer DL, Bruera E. Factors associated with the severity and improvement of fatigue in patients with advanced cancer presenting to an outpatient palliative care clinic. *BMC Palliat Care.* 2012;11(1):16. *PMC3515470*

5. Yennurajalingam S, Bruera E. Palliative management of fatigue at the close of life - "It feels like my body is just worn out". *Jama-J Am Med Assoc.* 2007;297(3):295-304.

6. Pollack LA, Rowland JH, Crammer C, Stefanek M. Introduction: charting the landscape of cancer survivors' health-related outcomes and care. *Cancer.* 2009;115(18 Suppl):4265-4269.

7. Peuckmann V, Elsner F, Krumm N, Trottenberg P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev.* 2010(11):CD006788.

8. Minton O, Stone P, Richardson A, Sharpe M, Hotopf M. Drug therapy for the management of cancer related fatigue. *Cochrane Database Syst Rev.* 2008(1):CD006704.

9. Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep.* 1985;69(7-8):751-754.

10. Mercadante S, Fulfaro F, Casuccio A. The use of corticosteroids in home palliative care. *Support Care Cancer.* 2001;9(5):386-389.

11. Loprinzi CL, Kugler JW, Sloan JA, et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol.* 1999;17(10):3299-3306.

12. Hanks GW, Trueman T, Twycross RG. Corticosteroids in terminal cancer--a prospective analysis of current practice. *Postgrad Med J.* 1983;59(697):702-706. *PMC2417686*

13. Metz CA, Robustelli Della Cuna G, Pellegrini A, Piazzi M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: A placebo-controlled, multicenter study. *European Journal of Cancer and Clinical Oncology.* 1989;25(12):1817-1821.

14. Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer.* 1974;33(6):1607-1609.

15. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol.* 2013;31(25):3076-3082.

16. Reddy S, Bruera E, Pace E, Zhang K, Reyes-Gibby CC. Clinically important improvement in the intensity of fatigue in patients with advanced cancer. *J Palliat Med.* 2007;10(5):1068-1075.

17. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev.* 2012;11:CD006145.

18. Piper BF, Lindsey AM, Dodd MJ. Fatigue mechanisms in cancer patients: developing nursing theory. *Oncol Nurs Forum.* 1987;14(6):17-23.

19. Mock V, St Ours C, Hall S, et al. Using a conceptual model in nursing research--mitigating fatigue in cancer patients. *J Adv Nurs.* 2007;58(5):503-512. *PMC2505113*

20. Yennurajalingam S, Palmer JL, Zhang T, Poulter V, Bruera E. Association between fatigue and other cancer-related symptoms in patients with advanced cancer. *Support Care Cancer.* 2008;16(10):1125-1130.

21. Barsevick A, Frost M, Zwinderman A, Hall P, Halyard M, Consortium G. I'm so tired: biological and genetic mechanisms of cancer-related fatigue. *Qual Life Res.* 2010;19(10):1419-1427. *PMC3031957*

22. Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol.* 2008;26(6):971-982. *PMC2770012*

23. Saligan LN, Olson K, Filler K, et al. The biology of cancer-related fatigue: a review of the literature. *Support Care Cancer.* 2015;23(8):2461-2478. *PMC4484308*

24. McNeely ML, Courneya KS. Exercise programs for cancer-related fatigue: evidence and clinical guidelines. *J Natl Compr Canc Netw.* 2010;8(8):945-953.

25. Yennurajalingam S F-HS, Delgado-Guay MO, Bull J, Bruera E. Dexamethasone (DM) for cancer-related fatigue: A double-blinded, randomized, placebo-controlled trial. *J Clin Oncol* 2012;Suppl.

26. Barsevick AM, Irwin MR, Hinds P, et al. Recommendations for high-priority research on cancer-related fatigue in children and adults. *J Natl Cancer Inst.* 2013;105(19):1432-1440. *PMC3888121*

27. Bruera E, Ernst S, Hagen N, et al. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. *Cancer Prev Control.* 1998;2(2):74-78.

28. 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(23):4439-4443.

29. 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(23):3475-3481.

30. Bruera E, Neumann CM, Pituskin E, Calder K, Ball G, Hanson J. Thalidomide in patients with cachexia due to terminal cancer: Preliminary report. *Ann Oncol.* 1999;10(7):857-859.

31. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol.* 2006;24(13):2073-2078.

32. Yennurajalingam S, Palmer JL, Chacko R, Bruera E. Factors associated with response to methylphenidate in advanced cancer patients. *Oncologist.* 2011;16(2):246-253. *PMC3228096*

33. Yennurajalingam S, Urbauer DL, Casper KL, et al. Impact of a palliative care consultation team on cancer-related symptoms in advanced cancer patients referred to an outpatient supportive care clinic. *J Pain Symptom Manage.* 2011;41(1):49-56.

34. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care.* 1991;7(2):6-9.

35. Bruera E, Michaud M, Vigano A, Neumann CM, Watanabe S, Hanson J. Multidisciplinary symptom control clinic in a cancer center: a retrospective study. *Support Care Cancer.* 2001;9(3):162-168.

36. de Raaf PJ, van der Rijt CC. Can you help me feel less exhausted all the time? *J Clin Oncol.* 2013;31(25):3056-3060.

37. Carmack Taylor CL, Demoor C, Smith MA, et al. Active for Life After Cancer: a randomized trial examining a lifestyle physical activity program for prostate cancer patients. *Psychooncology.* 2006;15(10):847-862.

38. Basen-Engquist K, Taylor CL, Rosenblum C, et al. Randomized pilot test of a lifestyle physical activity intervention for breast cancer survivors. *Patient Educ Couns.* 2006;64(1-3):225-234.

39. Basen-Engquist K, Scruggs S, Jhingran A, et al. Physical activity and obesity in endometrial cancer survivors: associations with pain, fatigue, and physical functioning. *Am J Obstet Gynecol.* 2009;200(3):288 e281-288. *PMC2666540*

40. 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(1):129-134.

41. American College of Sports Medicine. aLSP. *ACSM's Guidelines for Exercise Testing and Prescription.* Ninth edition ed: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014. p. 267-273

42. Fairey AS, Courneya KS, Field CJ, et al. Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: A randomized controlled trial. *Brain Behav Immun.* 2005;19(5):381-388.

43. Battaglini CL, Hackney AC, Garcia R, Groff D, Evans E, Shea T. The Effects of an Exercise Program in Leukemia Patients. *Integr Cancer Ther.* 2009;8(2):130-138.

44. Bower JE, Greendale G, Crosswell AD, et al. Yoga reduces inflammatory signaling in fatigued breast cancer survivors: A randomized controlled trial. *Psychoneuroendocrino.* 2014;43:20-29.

45. Bruera E, Yennurajalingam S, Palmer JL, et al. Methylphenidate and/or a nursing telephone intervention for fatigue in patients with advanced cancer: a randomized, placebo-controlled, phase II trial. *J Clin Oncol.* 2013;31(19):2421-2427. *PMC3691358*

46. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993;11(3):570-579.

47. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. *J Natl Cancer Inst.* 2008;100(16):1155-1166.

48. van Waart H, Stuiver MM, van Harten WH, et al. Effect of Low-Intensity Physical Activity and Moderate-to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial. *Journal of Clinical Oncology.* 2015;33(17):1918-U1990.

49. Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. *J Clin Epidemiol.* 2011;64(5):507-516. *PMC3076200*

50. Rothrock NE, Hays RD, Spritzer K, Yount SE, Riley W, Cella D. Relative to the general US population, chronic diseases are associated with poorer health-related quality of life as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS). *J Clin Epidemiol.* 2010;63(11):1195-1204.

51. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. *J Pain Symptom Manag.* 2004;27(1):14-23.

52. Johnston M, Pollard B, Hennessey P. Construct validation of the hospital anxiety and depression scale with clinical populations. *J Psychosom Res.* 2000;48(6):579-584.

53. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193-213.

54. Simmonds MJ. Physical function in patients with cancer: psychometric characteristics and clinical usefulness of a physical performance test battery. *J Pain Symptom Manage.* 2002;24(4):404-414.

55. Allgayer H, Nicolaus S, Schreiber S. Decreased interleukin-1 receptor antagonist response following moderate exercise in patients with colorectal carcinoma after primary treatment. *Cancer Detect Prev.* 2004;28(3):208-213.

56. Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. *Clin Chim Acta.* 2010;411(11-12):785-793.

57. Belizario JE, Fontes-Oliveira CC, Borges JP, Kashiabara JA, Vannier E. Skeletal muscle wasting and renewal: a pivotal role of myokine IL-6. *Springerplus.* 2016;5.

58. LaVoy EC, Fagundes CP, Dantzer R. Exercise, inflammation, and fatigue in cancer survivors. *Exercise immunology review.* 2016;22:82-93. *PMC4755327*

59. Gielen S, Adams V, Mobius-Winkler S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol.* 2003;42(5):861-868.

60. Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, Mendoza TR, Hay J, Atkinson TM, Abernethy AP, Bruner DW, Cleeland CS, Sloan JA, Chilukuri R, Baumgartner P, Denicoff A, St Germain D, O'Mara AM, Chen A, Kelaghan J, Bennett AV, Sit L, Rogak L, Barz A, Paul DB, Schrag D. Development of the national cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (pro-ctcae). *J Natl Cancer Inst* 2014;106.

61. Bennett AV, Dueck AC, Mitchell SA, Mendoza TR, Reeve BB, Atkinson TM, Castro KM, Denicoff A, Rogak LJ, Harness JK, Bearden JD, Bryant D, Siegel RD, Schrag D, Basch E. Mode equivalence and acceptability of tablet computer-, interactive voice response system-, and paper-based administration of the U.S. National cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (pro-ctcae). *Health Qual Life Outcomes* 2016;14:24.

62. Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, Atkinson TM, Bennett AV, Denicoff AM, O'Mara AM, Li Y, Clauser SB, Bryant DM, Bearden JD, 3rd, Gillis TA, Harness JK, Siegel RD, Paul DB, Cleeland CS, Schrag D, Sloan JA, Abernethy AP, Bruner DW, Minasian LM, Basch E. Validity and reliability of the us national cancer institute's patient- reported outcomes version of the common terminology criteria for adverse events (pro-ctcae). *JAMA oncology* 2015;1:1051-9.

63. Hauser, K., Walsh, D., Rybicki, L. A., Davis, M. P., & Seyidova-Khoshknabi, D. (2008). Fatigue in Advanced Cancer: A Prospective Study. *American Journal of Hospice and Palliative Medicine®*, *25*(5), 372–378. https://doi.org/10.1177/1049909108319267

64. Tina Noergaard Munch, Tao Zhang, Jie Willey, J. Lynn Palmer, and Eduardo Bruera. The Association between Anemia and Fatigue in Patients with Advanced Cancer Receiving Palliative Care. *Journal of Palliative Medicine* 2005 8:6, 1144-1149

65. Dunn A, Carter J, Carter H, Anemia at the end of life: prevalence, significance, and causes in patients receiving palliative care, *Journal of Pain and Symptom Management*, Volume 26, Issue 6,2003,Pages 1132-1139,ISSN 0885-3924,https://doi.org/10.1016/j.jpainsymman.2003.04.001. (http://www.sciencedirect.com/science/article/pii/S0885392403004202)

