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ORIGINAL ARTICLE

Anamorelin combined with physical activity, and nutritional counseling for cancer-related fatigue: a preliminary study

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Abstract

Purpose Cancer-related fatigue (CRF) is the most frequent and debilitating symptom in patients with advanced cancer. There are limited effective treatments for CRF. The objective of this prospective longitudinal study was to evaluate the change in CRF at Day 43 after treatment with combination therapy of oral Anamorelin 100 mg daily with physical activity and nutrition counseling.

Methods In this study, patients with CRF [≤ 34 Functional Assessment of Chronic Illness Therapy-Fatigue subscales(FACIT-F)] received Anamorelin 100 mg orally daily with standardized physical activity and nutrition counseling for 43 days. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Anorexia Cachexia(FAACT-ACS), Multidimensional Fatigue Symptom Inventory-Short Form(MFSI-SF), Patient-Reported Outcomes Measurement Information System(PROMIS-Fatigue), body composition, and physical performance tests were assessed at baseline, Day 15, 29, and 43. Frequency and type of side effects were determined by NCI CTAE 4.0.(NCT03035409).

Results 28/45 (62%) of patients dosed were evaluable at Day 43. The mean, SD for FACIT-F subscale improvement from baseline was 4.89 (± 13.07), P = .058, MFSI-SF (G) − 3.46 (± 6.86), **P = 0.013**, PROMIS-fatigue − 4.14 (± 7.88), **P = 0.010**, FAACT ACS 3.48 (± 8.13), **P = 0.035**. Godin Liesure-Time physical activity questionnaire 7.41 (± 16.50), **P = 0.038**. Weight (kg) 1.81 (± 2.63), **P = 0.005**, and Lean Body Mass 1.54 (± 1.85), **P = 0.001**, IGF-1 36.50 (± 48.76), **P = 0.015**. There was no significant improvement in physical performance outcomes. No adverse events > grade 3 related to the study drug were reported.

Conclusion The use of the combination therapy was associated with improvement of CRF (FACIT-F fatigue, PROMIS-fatigue, MFSI-SF-general), activity (Godin-leisure time), anorexia (FAACT), body composition, and IGF-1 levels. Further studies using combination therapy for CRF are justified.

Keywords Combination therapy · Physical activity · Nutritional counseling · Anamorelin · Cancer · Fatigue

Introduction

Cancer-related fatigue (CRF) is a frequent and serious consequence of cancer and cancer-related treatment [1, 2]. The frequency of CRF varies from 60 to 90% [3, 4]. Moderate to severe fatigue in advanced cancer patients is associated with poor quality of life outcomes, performance status scores, frailty, and poor overall survival [5–7]. Despite the prevalence and severity of CRF and its effects on the quality of life of patients with cancer, the number and efficacy of available treatment options are limited [8].

Several strategies have been proposed for the management of CRF, including physical activity, erythropoietin stimulating agents, and psychostimulants [8]. However,

Lay summary Cancer-related fatigue (CRF) is the most frequent and debilitating symptom in patients with advanced cancer. There are limited effective treatments for CRF. In this preliminary study, our group investigated the effects of the combination of oral Anamorelin 100 mg daily with physical activity and nutrition counseling on cancer fatigue and related outcomes. We found an improvement of patient reported fatigue, lack of appetite, and patient reported activity. We also found improvement in patient weight measures, and IGF-1 levels.

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there are few pharmacological studies which show sustained, clinically relevant benefits. Our group has shown that anti-inflammatory agents such as dexamethasone can result in clinically significant improvement of fatigue; however, due to their side-effect profile, steroids can only be given for a short duration [9, 10]. Physical activity is one of the best evidence-based approaches in patients with cancer, but its effect size for clinically relevant improvement of CRF has been low to modest at the best [11, 12].

Prior studies found that a selective ghrelin receptor agonist, Anamorelin, was an effective therapeutic agent in the treatment of cancer cachexia in NSCLC patients [9–13]. The rationale for this study was based on the improvement in CRF in prior randomized control studies investigating Anamorelin for lean body mass, and anorexia [9–17]. However, there were major limitations in terms of the assessment of CRF in these studies. The limitations include (a) None of these prior studies were conducted using the change in CRF as a primary outcome, or co-primary outcome; (b) Factors such as patients' physical activity and diet, which can have beneficial effects for cachexia and CRF, were not controlled in the design of these studies; and (c) Patient population was not well characterized (e.g. patients with fatigue potentially stemming from multiple mechanisms, such as depression, anxiety, inflammation, or anemia, were included).

On the basis of its known mechanisms — specifically, effects on inflammation, improvement in lean body mass, and appetite via ghrelin activity — we hypothesized that Anamorelin, in combination with a standardized physical activity intervention and nutrition counseling, could improve CRF [15, 16, 18]. Therefore, the goal of this study was to evaluate the effects of a combination of oral Anamorelin (100 mg daily) with physical activity and nutrition counseling on the change in CRF scores at day 43.

Materials and methods

The University of Texas MD Anderson Cancer Center Institutional Review Board approved the protocol, and all patients were provided written informed consent (NCT03035409).

Patients

In this longitudinal prospective study, consecutive patients were approached by a research nurse in the outpatient centers for supportive care and oncology at the University of Texas MD Anderson Cancer Center in Houston, Texas. Patients' eligibility for this study included: (a) Presence of advanced cancer (metastatic, or recurrent, incurable cancer), (b) Presence of fatigue as assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) of ≤ 34 on a 0 to 52 scale (in which 52 = no fatigue, and 0 = worst possible fatigue), (c) Presence of fatigue for a minimum of 2 weeks prior to screening, (d) Presence of C-reactive protein (CRP) levels ≥ 3 mg/l in the absence of any other more likely cause of increased CRP (like an infection or an autoimmune disorder), (e) No evidence of moderate to severe depression as determined by a score ≤ 13 on the Hospital Anxiety Depression Scale (HADS) or uncontrolled pain, (f) Presence of unintentional weight loss ranging from ≥ 2 to $\leq 15\%$ at any time within the last 12 months, (g) Hemoglobin level of ≥ 9 g/dl, and (h) No contraindications to Anamorelin, and physical activity including uncontrolled diabetes milletus. We excluded patients with hypothyroidism, pregnant or lactating women, male patients with history of hypogonadism, prostate cancer, and patients who are regularly engaged in moderate or vigorous-intensity exercise at least 5 times a week.

Interventions

Eligible patients who agreed to participate in the study were given a 43-day supply of Anamorelin 100-mg tablets (Helsinn Therapeutics, Iselin, NJ, USA). Patients were prescribed to take 1 tablet orally daily while fasting (at least 1 h before a meal). All patients receiving Anamorelin also received a standardized exercise prescription and nutritional support. The rationale for standardized physical activity and nutritional support was that these are two important, evidence-based interventions for the management of fatigue [8, 10], but both have only modest effects on improvement of CRF [10],11]. Thus, Anamorelin was used to potentiate the effects of these interventions so to provide a robust response.

Exercise prescription

The standardized exercise prescription for this study was based on the American College of Sports Medicine (ACSM) exercise recommendations for cancer patients to ensure safety and maximal benefit [19]. The exercise intervention included (a) resistance training 3 days per week, and (b) moderate intensity walking for up to 150 min per week. At the first supervised session the patient performed the resistance exercises, and moderate intensity walking up to 30 min, depending on the patient's tolerance. The resistance exercise program was designed to strengthen the major muscles of the lower body, including the quadriceps, hamstrings, gluteus maximus, and hip flexor group. These exercises included (but were not be limited to) squats, lunges, leg extensions, leg curls, and hip extensions. We used resistance tubes as our mode of providing resistance exercises. These tubes are color-coded to indicate their specific resistance level: light, moderate, or

hard. The resistance exercise sessions are to be completed 3 days a week, allowing at least 48 h between each session. The participant began with 1 set of 10 to 12 repetitions at the lightest resistance progressing to 2 sets of 12 repetitions as exercise tolerance increases. Resistance was then increased as the participant's endurance and strength progressed. For the graded resistance program the individual began with a lighter resistance and progressed to heavier resistance once a level has been mastered. The participant began with 2 sets of 12 repetitions at the next established intensity level. Since the level of aerobic fitness was expected to vary among participants, the frequency and duration of the walking program were established based on the exercise physiologist's assessment of the participant's baseline aerobic fitness level using the six-minute walk test [20]. To encourage and monitor adherence to the walking program, we provided participants with a pedometer and an exercise log to record their resistance exercise sessions, time spent in moderate intensity walking, and the number of steps they take each day. Participants were asked to walk a minimum of 5 days a week at the duration established by the exercise physiologist. In the first week of the intervention and Day 21(± 3 days), the exercise physiologist met with each participant in person to evaluate his or her current strength and aerobic fitness level and supervise the assigned exercises. Each week, the exercise physiologist assessed their progress on telephone and helped them identify and overcome any barriers to completing the exercise program, and to evaluate for adverse events or health problems. The frequency, intensity, and duration of the assigned exercises were also be evaluated and adjusted as necessary.

Nutrition counseling

All patients enrolled in this study received 2 sessions of detailed nutritional counseling encounters by a dietitian. One session was conducted at baseline and the 2nd at day 21(± 3). The plan was to achieve a goal of 1.5 × Resting Energy Expenditure (REE) as estimated by the Mifflin St. Jeor method [21]. Frequent small meals that are calorie dense were recommended. Patients with taste disturbance received a trial of Zinc 220 mg orally daily for 4 weeks. Commercially available specific amino acids preparations rich in arginine, glutamine, and leucine-related products, such as Beta hydroxyl Beta methylbutyrate, were advised by a nutritionist to assist patients achieve calorie goals and maintain lean body mass [22].

Adherence to the Anamorelin was calculated by the proportion of prescribed pills (43 pills) taken during the study period (6 weeks). Adherence to PA was calculated by the percentage completion of total prescribed counseling (7 sessions), resistance exercises (at least 2 sets of exercises every week), and walking minutes (at least 90 min every week) for 6 weeks. Adherence to nutritional counseling sessions and dietary recommendation was calculated by the percentage completion of the counseling sessions prescribed (2 sessions) for 6 weeks, and actual percentage intake of prescribed calories, and protein per day at Day 21 and Day 43.

Outcome measures

Patients' demographic data, including age, sex, ethnicity, cancer diagnosis, and education level were recorded at the time of study entry. The FACIT and its fatigue subscale (FACIT-F), the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), the Patient Reported Outcome Measurement Information System-fatigue (PROMIS-fatigue), the Edmonton Symptom Assessment Scale (ESAS)-fatigue item, Godin Leisure-Time physical activity questionnaire, and the Functional Assessment of Anorexia-Cachexia Therapy Anorexia/Cachexia Scale (FAACT-A/CS) were assessed at baseline, Day 15, Day 29, and Day 43. Body composition, and laboratory correlates including prealbumin, albumin, fasting blood glucose, Insulin-like growth factor-1 (IGF-1), and C-reactive protein were measured. Exploratory outcomes included the ESAS, HADS, Pittsburgh Sleep Quality Index (PSQI), physical performance outcomes, mean daytime activity assessed by Actigraphy, and Global symptom evaluation.

FACIT-F fatigue subscale

The FACIT-F fatigue subscale allows patients to rate the intensity of their fatigue using a 0–4 scale (0 = not at all, 4 = very much) during the previous 7 days. Test–retest reliability coefficients for this scale ranges from 0.84 to 0.90, and minimally clinically important difference is 3.5 points [23].

MFSI-SF consists of 30 items designed to assess the multidimensional nature of fatigue [24]. Ratings are summed to obtain scores for 5 subscales (general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor) during the previous week.

PROMIS The PROMIS F-SF consists of seven items that measure both the experience of fatigue and the interference of fatigue on daily activities over the past week [25]. Response options are on a 5-point Likert scale, ranging from 1 = never to 5 = always, with higher scores indicating greater fatigue [25].

The **FAACT-A/CS** subscale is a 12-item symptom-specific subscale designed to measure patients' symptoms and concerns about their anorexia /cachexia during the previous 7 days. The FAACT has internal consistency and a reliability coefficient (Cronbach's alpha) of 0.88 for the 12 components [26].

The **ESAS** measures 10 common symptoms in the past 24 h (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well-being).This questionnaire has been found to be valid and reliable in cancer populations [27].

The **PSQI** is a 19-item questionnaire and is a validated instrument in measuring the quality and patterns of sleep [28]. The PSQI global score ranges from 0 to 21, with a score of 5 or greater indicating significant sleep disturbance.

Global symptom evaluation

At the end of the study (Day 43), patients were asked about their fatigue (worse, about the same, or better) after starting the intervention.

Physical performance tests

The ***30 s sit-to-stand task*** was used to assess lower body strength [29]. On the start signal, the participant rises to a full stand and then returns to a fully seated position. The patient completes as many full stands as possible within a 30 s period.

In the ***six-minute walk test***, participants were asked to walk as fast and as far as they can for six minutes, and the distance walked is measured. [30]. The six minute walk test was performed as per the ATS guidelines (https://www.thoracic.org/statements/resources/pfet/sixminute.pdf.)

Actigraphy

We analyzed mean daytime activity (MDTA) assessed using actigraphy (ActiGraph wGT3X, Actigraph, Pensicola, Florida).

The Godin Leisure-Time physical activity questionnaire asks participants how many times per week on average do they participate in strenuous, moderate and mild exercises for more than 15 min during their free time [31].

Body composition

All patients were assessed for body composition using the InBody 770 (Inbody Co., LTD, Cerritos, CA, USA), at baseline and Day 43 [32, 33].The InBody utilizes bioimpedence impedance analysis (BIA) method to measure body composition. The InBody 770 is a direct segmental (right

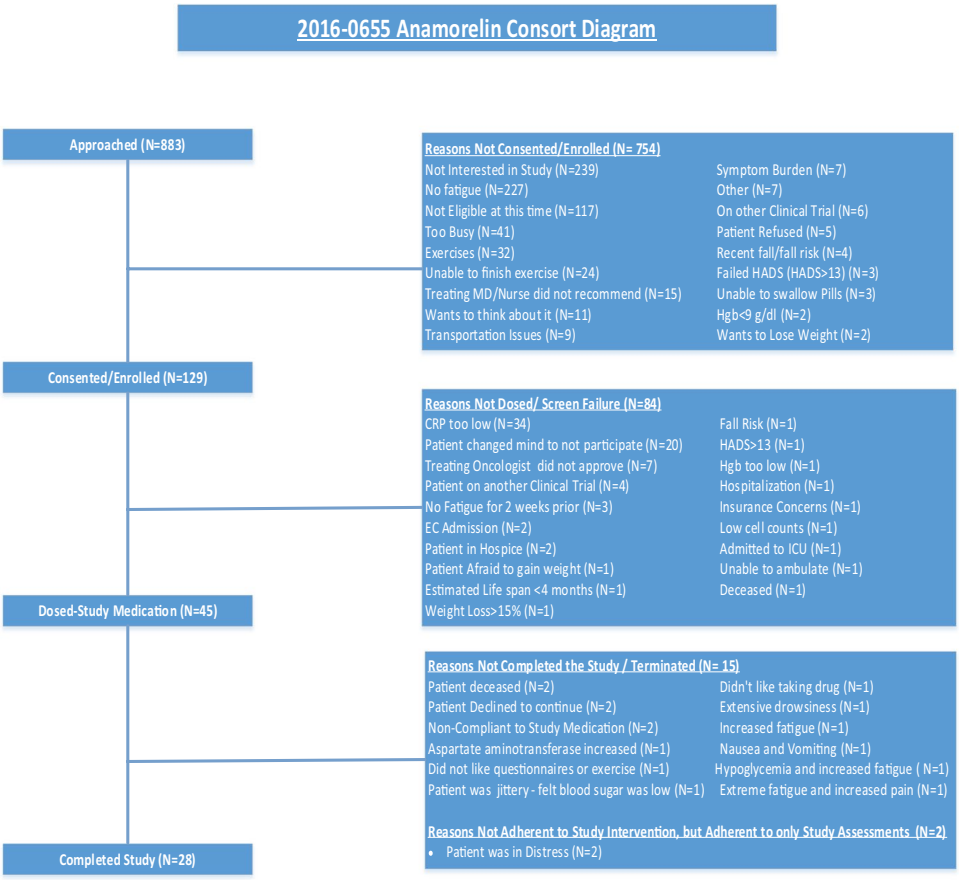

Fig. 1 CONSORT diagram depicting patient flow throughout the study

Table 1 Baseline demographics, clinical, and laboratory characteristics

Characteristic	N (%),(N = 28)	
Age in years (Median)	64	
Gender		
Male	18 (64.3)	
Race		
White	23 (82.1)	
African American	3 (10.7)	
Asian	2 (7.1)	
Marital status		
Single/Never married	2 (7.1)	
Married	21 (75.0)	
Divorced	3 (10.7)	
Widowed	2 (7.1)	
Employment status		
Full time	12 (46.2)	
Retired	8 (30.8)	
Homemaker	1 (3.9)	
Unemployed	5 (19.2)	
Primary diagnosis		
Lung Cancer		
- Non-Small Cell Lung cancer	13 (46.4)	
- Small Cell Lung Cancer	2 (7.14)	
- Other Type of Lung Cancer	2 (7.14)	
Gastrointestinal		
Bile duct	2 (7.14)	
Colon	2 (7.14)	
Pancreas	2 (7.14)	
Breast Cancer	2 (7.14)	
Gynecological	2 (7.14)	
Head & Neck	1 (3.6)	
Currently receiving treatment		
Currently on Chemotherapy	16 (64.0)	
Currently on Immunotherapy	5 (20.0)	
Recently on Radiation therapy (in past 30 days)	3 (12.0)	
Currently on Targeted therapy	1 (4.0)	
Surgery	0 (0.0)	
No Treatments	0 (0.0)	
Zubrod Performance Status		
0	1 (3.6)	
1	15 (53.6)	
2	12 (42.8)	
Assessments	**Mean (SD)**	**Median (IQR)**
FACIT-F Subscale	23.0 (±7.7)	21.5 (17.5, 28.8)
MFSI-SF		
General fatigue	15.5 (±4.6)	15.5 (12.0, 18.5)
Physical fatigue	7.5 (±3.9)	6.5 (5.0, 9.8)
Emotional fatigue	4.6 (±4.0)	4.0 (1.0, 7.8)
Mental fatigue	5.9 (±4.2)	6.0 (2.25, 8.8)
Vigor	10.3 (±3.6)	10.0 (8.0, 12.0)
MFSI-Total	23.3 (±14.8)	23.5 (12.3, 32.3)
PROMIS		

Table 1 (continued)

Characteristic	N (%),(N = 28)	
PROMIS-Fatigue	61.4 (±4.6)	60.6 (57.8, 65.9)
ESAS		
Fatigue	5.5 (±2.8)	6 (3.25, 7)
HADS		
Anxiety	5.0 (±3.5)	4.5 (2.0, 6.0)
Depression	6.3 (±3.7)	6.0 (3.25, 8.75)
HADS Total	11.3 (±6.4)	12.0 (6.0, 14.0)
PSQI (N = 15)	9.8 (±3.8)	10.0 (7.0, 12.0)
Physical performance measures		
Godin Leisure-Time Physical Activity Questionnaire	12.3 (±10.7)	9 (3,19)
30 s sit and stand test	9.2 (±4.0)	10 (7, 12)
Six-minute walk test	441.9 (±121.6)	440 (390.3, 515)
Actigraphy		
Mean Daytime Activity (MDTA)	367 (±188.8)	349 (245, 425)
Body composition (Inbody Measures)		
Weight (kg)	77.3 (±18.1)	75.1 (64.9, 89.9)
BMI	25.5 (±4.9)	26.1 (21, 28.4)
Body fat %	29.9 (±10.2)	27.9 (22.3, 37.6)
Body fat mass (kg)	23.6 (±10.9)	23.0 (16.0, 29.3)
Fat-free mass (kg)	16.7 (±14.6)	13.9 (11.8, 16.9)
Lean body mass (kg)	52.4 (±11.7)	51.3 (43.1, 63.9)
Skeletal muscle mass (kg)	28.4 (±6.8)	27.4 (22.7, 34.8)
Skeletal muscle mass index	9.6 (±1.5)	9.6 (8.5,10.3)
Total body water (kg)	39.0 (±8.5)	37.9 (32.5, 47.4)
Ratio of Extracellular Water to Total body water[a]	0.4 (±0.01)	0.4 (0.3, 0.4)
Whole body phase angle	4.3 (±0.6)	4.25 (3.80, 4.65)
Caloric intake	1572.1 (±370.5)	1570 (1405, 1795)
Resting energy expenditure	304.9 (±377.7)	228 (200, 270)
Laboratory correlates		
Albumin, g/dL	4.1 (±0.4)	4.1 (3.8, 4.4)
Prealbumin, mg/dL	20.7 (±6.0)	20.8 (17.6, 24.5)
Fasting blood glucose, mg/dL	123.3 (±42.7)	106.0 (95.0, 140.0)
IGF-1, mcg/mL	126.9 (±66.7)	133.0 (69.5, 156.0)
C-reactive protein, mg/L	24.7 (±33.1)	8.4 (5.4, 32.9)

Abbreviations: *FACIT-F*, Functional Assessment of Chronic Illness Therapy–Fatigue subscale; *MFSI-SF*, Multidimensional Fatigue Symptom Inventory-Short Form; *PROMIS*, Patient-Reported Outcomes Measurement Information System-Fatigue; *ESAS*, Edmonton Symptom Assessment Scale; *HADS*, Hospital Anxiety Depression Scale; *PSQI*, Pittsburgh Sleep Quality Index; *IGF-1*, Insulin-Like Growth Factor-1; *IQR*, interquartile range; *SD*, Standard Deviation

[a]Ratio of Extracellular Water to Total body water = Extra cellular water/Total body water

arm, left arm, trunk, and right leg, left leg), multifrequency BIA system.

Laboratory correlates

Laboratory correlates including prealbumin, albumin, fasting blood sugar, C-reactive protein (CRP), and Insulin growth factor-1 (IGF-1) [15, 17]. Frequency and type of side effects were determined by NCI CTAE 4.0.

Statistical analysis

Standard summary statistics were used to summarize the demographic and clinical characteristics for all patients enrolled in the pilot study. We calculated the mean change in FACIT-F fatigue subscale, MFSI-SF, ESAS fatigue item, and PROMIS-fatigue from baseline to Day 43. Similar analyses were calculated for the secondary subjective outcomes. A sample size of 30 evaluable was used as we can detect a mean change = 4.0 (assuming Normal data,

80% power and a two-sided 5% alpha, and a 7.5 standard deviation of differences) [13]. A Cohen's D was analyzed to assess the preliminary effects of combination therapy. A linear mixed model was also conducted to assess an overall time trend of FACIT-F fatigue subscale scores. A p-value of ≤ 0.05 was considered statistically significant. All statistical analysis was performed using Stata/MP v16.0 (College Station, TX, USA), or IBM SPSS 26 (Armonk, NY, USA).

Results

Figure 1 shows complete details of patient study enrollment and completion.

129 patients were consented to evaluate eligibility and, if eligible, to participate in this study. Of those, 84 did not meet the eligibility criteria.

As described above, 28 patients were evaluable for the primary outcome measures (fatigue) at Day 43. The mean % adherence (SD) to study medication was 95% (± 9.7), physical activity [counseling 81% (23) walking exercise 67.3% (± 32.9), resistance exercise using resistance tube 56% (± 35.2)], nutritional counseling was 98.2 (± 9.4), dietary recommendation was 78.6% (± 25.5%) for calories/day, and 61.7%(± 23.5%) for protein/day on Day 21 (3 weeks); 91.6% (± 23.4%) for calories/day, and 72.4% (± 20.0%) for protein/day on Day 43 (6 weeks). Table 1 summarizes patient demographic characteristics and baseline symptoms. Majority of the patients were have ECOG performance status of 1 (n = 15, 54%) or 2 (n = 12, 43%) at baseline. The baseline FACIT-F fatigue subscale [median (IQR)] was 21.5 (17.5, 28.8); MFSI-SF general was 15.5 (12.0, 18.5); and PROMIS-fatigue was 60.6 (57.8, 65.9).

Table 2 shows the mean change values for fatigue measures. The mean (SD) change for the FACIT-F Fatigue subscale was 4.89 (± 13.07), P = 0.058 (0.37); the mean change for the MFSI-SF general fatigue was − 3.46 (± 6.86), P = 0.013 (− 0.51). For PROMIS-fatigue, the mean change was − 4.14 (± 7.88), P = 0.010 (− 0.53). Supplementary Fig. 1 shows mean fatigue scores over time from baseline to Day 43.

Supplementary Fig. 2 shows the linear mixed model adjusted prediction of FACIT-F over time. We found that there was a significant time effect with FACIT-F increasing on average of 0.11 (95% CI: 0.03–0.19; P = 0.007) units per day. Similarly, when time was added as a categorical variable in our model, our 43-day measure had

Table 2 Changes in cancer-related fatigue from baseline at Day 15, Day 29, and Day 43 after combination therapy

Outcome measure	Day 15—Baseline (N = 28)		Day 29—Baseline *(N = 28)*		Day 43—Baseline *(N = 28)*	
	Mean (± SD), (CI)	P-value* (Cohen's D)	Mean (± SD), (CI)	P-value* (Cohen's D)	Mean (± SD), (CI)	P-value* (Cohen's D)
FACIT-F Fatigue Subscale	3.89 (± 8.71), (0.52, 7.27)	***0.025*** (0.45)	6.32 (± 9.53), (2.63, 10.02)	***0.002*** (0.66)	4.89 (± 13.07), (− 0.18, 9.96)	*0.058 (0.37)*
ESAS-Fatigue	− 0.68 (± 2.87), (− 1.79, 0.43)	*0.22 (− 0.24)*	− 0.75 (± 2.70), (− 1.80, 0.30)	*0.15 (− 0.28)*	− 0.81 (± 2.87), (− 1.95, 0.32)	*0.15 (− 0.28)*
MFSI-SF						
General fatigue	− 2.25 (± 4.53), (− 4.01, − 0.49)	***0.014*** *(− 0.50)*	− 4.18 (± 5.74), (− 6.40, − 1.95)	***0.001*** *(− 0.73)*	− 3.46 (± 6.86), (− 6.21, − 0.81)	***0.013*** *(− 0.51)*
Physical fatigue	− 0.71 (± 3.69), (− 2.15, 0.72)	*0.31 (− 0.19)*	− 0.50 (± 4.43), (− 2.22, 1.22)	*0.56 (− 0.11)*	− 0.39 (± 5.03), (− 2.34, 1.56)	*0.68 (− 0.08)*
Emotional fatigue	− 0.43 (± 2.20), (− 1.28, 0.43)	*0.31 (− 0.19)*	0.14 (± 3.15), (− 1.08, 1.36)	*0.81* (0.05)	1.04 (± 4.36), (− 0.65, 2.73)	*0.22* (0.24)
Mental fatigue	− 0.93 (± 2.57), (− 1.92, 0.07)	*0.07* (− 0.36)	− 1.39 (± 2.90), (− 2.52, − 0.27)	***0.017*** (− 0.48)	− 0.36 (± 4.12), (− 1.95, 1.24)	*0.65* (− 0.09)
Vigor	0.46 (± 2.89), (− 0.65, 1.58)	*0.40* (0.16)	0.39 (± 3.46), (− 0.95, 1.73)	*0.55* (0.11)	− 1.11 (± 5.28), (− 3.15, 0.94)	*0.28* (− 0.21)
MFSI-SF totals	− 4.79 (± 9.59), (− 8.50, − 1.07)	***0.017*** [a] (− 0.50)	− 6.32 (± 12.41), (− 11.53, − 1.51)	***0.012*** (− 0.51)	− 2.07 (± 17.59), (− 8.89, 4.75)	*0.54* (− 0.12)
PROMIS-Fatigue	− 2.74 (± 6.12), (− 5.11, − 0.37)	***0.025*** *(− 0.45)*	− 3.64 (± 8.22), (− 6.82, − 0.45)	***0.027*** (− 0.44)	− 4.14 (± 7.88), (− 7.19, − 1.08)	***0.010*** *(− 0.53)*

Abbreviations: *FACIT-F*, Functional Assessment of Chronic Illness Therapy–Fatigue subscale; *ESAS*, Edmonton Symptom Assessment Scale; *MFSI-SF*, Multidimensional Fatigue Symptom Inventory-Short Form; *PROMIS*, Patient-Reported Outcomes Measurement Information System–Fatigue; *SD*, Standard Deviation; *CI*, Confidence Interval, Lower and Upper Confidence Interval; *P-values are derived using Paired sample t-test; [a]P values were derived using Wilcoxon Signed Rank Test. Bolded P-value indicates statistically significant

a significant increase from baseline of 4.89 (95% CI: 0.67–9.11); P = 0.023.

Tables 3 and 4 show body composition and related outcomes. From baseline to Day 43, the mean change for FAACT ACS was 3.48 (± 8.13), P = 0.035 (0.43), and for the Godin Leisure-time physical activity questionnaire was 7.41 (± 16.50), P = 0.038 (0.45). Among the physical measures, the mean change in weight (kg) was 1.81 (± 2.63), P = 0.005 (0.69), in Lean Body Mass was 1.54 (± 1.85), P = 0.001 (0.84), and in level of IGF-1 was 36.50 (± 48.76), P = 0.015 (0.75). No significant improvements from baseline in the physical performance and actigraphy measure for daytime active (mean daytime activity) were found. Global Symptom evaluation scores show that 22/25 (88%) reported that the combined interventions were better or same (Table 3). No adverse > grade 3 events related to the study drug were reported (Table 5).

Discussion

The results of this preliminary study showed that the combination of Anamorelin, physical activity and nutrition counseling was safe, tolerable. The results also suggested that patient reported subjective outcomes for CRF, appetite, leisure-time physical activity, and body composition improved with combination therapy for 6 weeks. The results of this study, performed in advanced cancer patients with mixed cancer types, are consistent with the results in the anorexia and body composition measures observed in previous studies on cachexia using Anamorelin in lung cancer patients [14–18]; however, these previous cachexia-focused studies did not control for exercise and nutritional counseling.

The effect size (0.37) for improvement in CRF was significantly larger in our study, compared to previous work

Table 3 Changes in exploratory measures at Day 15, Day 29, and Day 43 after combination therapy

Outcome measure	Day 15—Baseline (N = 28)		Day 29—Baseline *(N = 28)*		Day 43—Baseline *(N = 28)*	
	Mean (± SD), CI	P-value* (Cohen's D)	Mean (± SD), CI	P-value* (Cohen's D)	Mean (± SD), CI	P-value* (Cohen's D)
FACT-G Total	0.59 (± 9.17), (− 2.96, 4.15)	*0.74 (0.06)*	1.31 (± 8.97), (− 2.17, 4.79)	*0.45 (0.15)*	− 1.10 (± 10.71), (− 5.26, 3.05)	*0.59 (− 0.10)*
FAACT-A/CS Total	1.70 (± 4.89), (− 0.23, 3.64)	*0.082 (0.35)*	4.53 (± 5.54), (2.34, 6.72)	***< 0.001*** *(0.82)*	3.48 (± 8.13), (0.27, 6.70)	***0.035*** [a] *(0.43)*
ESAS-Appetite	− 0.43 (± 3.06), (− 1.62, 0.76)	*0.47 (− 0.14)*	− 1.04 (± 3.19), (− 2.27, 0.20)	*0.097 (− 0.32)*	− 0.56 (± 3.07), (− 1.77, 0.66)	*0.35 (− 0.18)*
PSQI (N = 15)			-0.09 (± 4.18), (-2.90, 2.72)	*0.94 (-0.02)*	-0.09 (± 2.12), (-1.51, 1.33)	*0.89 (-0.04)*
Godin Leisure Test Total					7.41 (± 16.50), (0.09, 14.72)	***0.038*** [a] *(0.45)*
Global Symptom Evaluation						
– Better N (%)					13 (52%)	
– About the same N (%)					9 (36%)	
– Worse N (%)					3 (12%)	

Laboratory measure	**Day 21—Baseline *(N = 28)***		**Day 43—Baseline *(N = 28)***	
	Mean (± SD), (CI)	**P-value* (Cohen's D)**	**Mean (± SD), (CI)**	**P-value* (Cohen's D)**
Albumin, g/dL	− 0.10 (± 0.23), (− 0.20, − 0.01)	***0.036*** *(− 0.45)*	− 0.05 (± 0.36), (− 0.20, 0.10)	*0.47 (− 0.15)*
Prealbumin, mg/dL	-0.07 (± 3.94), (− 1.82, 1.68)	*0.94 (− 0.02)*	0.10 (± 3.83), (− 1.70, 1.89)	*0.91 (0.02)*
Fasting Blood glucose, mg/dL	22.92 (± 61.52), (− 2.47, 48.31)	*0.07 (0.37)*	7.04 (± 44.4), (− 11.71, 25.79)	*0.45 (0.16)*
IGF-1, mcg/mL	58.4 (± 59.4), (− 24.05, 92.67)	***0.001*** [a] *(0.98)*	36.50 (± 48.76), (8.35, 64.65)	***0.02*** [a] *(0.75)*
C-Reactive Protein, mg/L	3.52 (± 47.61), (− 16.13, 23.18)	*0.71 (0.07)*	2.11 (± 48.36), (− 17.85, 22.07)	*0.31* [a] *(0.04)*

Abbreviations: *FACT-G*, Functional Assessment of Cancer Therapy-General; *FAACT*, Functional Assessment of Anorexia and Cachexia Therapy-Anorexia/Cachexia Scale; *ESAS*, Edmonton Symptom Assessment Scale; *PSQI*, Pittsburgh Sleep Quality Index; *IGF-1* Insulin Like growth factor-1; *SD*, Standard Deviation; *CI*, Confidence Interval, Lower and Upper Confidence Interval; * P-values derived using Paired sample t-test; [a]P-values derived using Wilcoxon Signed Rank Test. Bolded P-value indicates statistically significant

where effect sizes were 0.16 in the Romana 1 study, 0.008 in the Romana 2 study, and 0.057 in a study by Katakami et al. [14–18]. The larger effect size we observed could be due to several differences between our study and these previous works. In our study, the change in CRF was the primary outcome, so we studied a more homogeneous patient population: only patients with clinically significant fatigue, along with inflammation (increase in C-reactive protein), weight loss, and low levels of pain, anxiety, and depression, were selected. Other relevant differences include the timepoint assessed (the ROMANA study utilized week 12) and the cancer types included (ROMANA and Katakami included only patients with non-small cell lung cancer) [15, 16]. However, the most obvious difference in the study described here is the addition of a standardized exercise intervention and nutritional counseling, which may reduce variability in physical activity and dietary intake among participants and work with Anamorelin to potentially maximize its benefits. This strongly suggests that the addition of a standardized physical activity intervention and nutritional counseling in combination with Anamorelin may be partially responsible for this improvement of effect size. Our results suggest that future studies of Anamorelin's impact on CRF are warranted and should be conducted in combination with physical activity and nutritional supplementation. It was encouraging that the combination therapy significantly improved patient reported CRF, Godin Leisure-Time physical activity scores, body composition, and anorexia scores [34]. However, further randomized controlled studies are needed to understand the mechanism of action of combination therapy on CRF.

Prior studies conducted by our team and others found significant improvement in CRF with the use of anti-inflammatory agents such as corticosteroids (effect size 0.59); however, this benefit is limited to two weeks of use due to side-effects [12]. Thus, there are additional advantages to using Anamorelin instead anti-inflammatory agents like corticosteroids: first, Anamorelin can be used for longer periods; and second, Anamorelin can be used in the increasing number of patients receiving immunotherapy, since corticosteroids are avoided in patients receiving immunotherapy due to potential interactions. This second characteristic of Anamorelin makes it a promising agent at a time when the majority of cancer patients receive immunotherapy at some point in the trajectory of their disease. Compared to prior studies, our study using a combination of Anamorelin with physical and nutritional counseling found improvements in body composition including lean body mass, but our results differ from other studies due to possible reasons which include: (a) a very focused population of advanced cancer patients with mixed cancer types; (b) Eligibility criteria that specified the presence of clinically significant fatigue, weight loss, and inflammation [10, 12, 13].

In our study, even though we found significant improvement in the Godin Leisure-Time physical activity questionnaire (subjective), we did not observe any significant improvement in the physical performance tests and mean daytime activity (an activity measure assessed using actigraphy) associated with the use of the combination therapy. Prior studies by our team and others found a similar disconnect between subjective and objective measures in prior fatigue studies [35, 36]. This finding suggest that activity alone might not

Table 4 Changes in Body Composition Scores (Inbody Measures) from Baseline at Day 43 after Combination Therapy[b]

Inbody measures	Day 43—Baseline (N = 28)	
	Mean (± SD), (CI)	P-value* (Cohen's D)
Weight (kg)	*1.81 (± 2.63), (0.61, 3.00)*	***0.005*** *(0.69)*
BMI	0.60 (± 0.80), (0.23, 0.96)	***0.003*** (0.74)
Body Fat %	0.01 (± 2.23), (− 1.01, 1.02)	*0.98 (0.00)*
Body Fat Mass (kg)	0.49 (± 2.04), (− 0.44, 1.42)	*0.28 (0.24)*
Fat free Mass (kg)	− 2.95 (± 14.48),(− 9.55, 3.64)	*0.36* [a] *(-0.20)*
Lean body Mass (kg)	1.54 (± 1.85), (1.50, 5.31)	***0.001*** *(0.84)*
Skeletal Muscle mass (kg)	0.96 (± 1.10), (0.45, 1.48	***0.001*** (0.87)
Skeletal Muscle Mass Index	0.32 (± 0.35), (0.15, 0.48)	***0.001*** (0.90)
Total Body Water (kg)	1.16 (± 1.35), (0.53, 1.79)	***0.001*** [a] (0.86)
Ratio of water to body water	0.18 (± 0.80), (− 0.20, 0.55)	*0.33 (0.22)*
Whole body angle	0.07 (± 0.23), (− 0.04, 0.18)	*0.19 (0.30)*
Caloric intake	246.4 (± 416.9), (15.55, 477.25)	***0.038*** [a] *(0.59)*
Resting Energy Expenditure	− 102.1 (± 470.1), (− 373.47, 169.33)	*0.27 (0.56)*

Abbreviations: *SD*, Standard Deviation; *CI*, Confidence Interval, Lower and Upper Confidence Interval; * P-values were derived using Paired sample t-test; [a]P values were derived using Wilcoxon Signed Rank Test. BMI, Body Mass Index; [b]Assessed using InBody Measures

Table 5 Frequency and severity of adverse events (AE) reports in the combination therapy study[a] (N = 28)*

Adverse event[c]	Any AE Grade ≤ 3 Events		Any AE Grade > 3	
	No. of patients with AE (X (X/N)[b]	Total no. of AE = 137	No. of patients with AE (Y (Y/N)[b]	Total no. of AE = 4
Diarrhea	5 (18)	10	0	0
Fatigue	10 (36)	10	0	0
Hyperglycemia	4 (14)	10	1(4)	1
Anorexia	6 (21)	8	0	0
Insomnia	6 (21)	8	0	0
Nausea	7 (25)	8	0	0
Dizziness	4 (14)	7	0	0
Dyspnea	4 (14)	5	0	0
Abdominal pain	3 (11)	4	0	0
Fever	3 (11)	4	0	0
Pain	1 (4)	4	0	0
Pain in extremity	3 (11)	4	0	0
Paresthesia	3 (11)	4	0	0
Upper respiratory infection	3 (11)	4	0	0
Arthralgia	3 (11)	3	0	0
Back pain	3 (11)	3	0	0
Constipation	2 (7)	3	0	0
Peripheral sensory neuropathy	2 (7)	3	0	0
Rash maculopapular	2 (7)	3	0	0
Chest wall pain	1 (4)	2	0	0
Cough	2 (7)	2	0	0
Death NOS	0	0	2 (7)	2
Dry eye	1 (4)	2	0	0
Dry mouth	2 (7)	2	0	0
Dry skin	2 (7)	2	0	0
Dysgeusia	2 (7)	2	0	0
Facial pain	2 (7)	2	0	0
Fall	2 (7)	2	0	0
Flatulence	2 (7)	2	0	0
Flushing	2 (7)	2	0	0
Gait disturbance	1 (4)	2	0	0
Headache	2 (7)	2	0	0
Hypertension	2 (7)	2	0	0
Myalgia	2 (7)	2	0	0
Non-cardiac chest pain	2 (7)	2	0	0
Vomiting	1 (4)	2	0	0
Hyponatremia	0	0	1 (4)	1

[a]For a given patient there may be multiple adverse events at different time points. [b] X(X/N), X = number of patients with particular AE ≤ 3 grade; Y(Y/N), Y = number of patients with particular AE ˃3 grade, N = total number of patients, 28. [c]Adverse events were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4; [c]No severe (≥ grade 3) adverse events related to the study drug were reported. No patient had to dose reduce due to the study intervention

be an optimal outcome to pursue for future clinical trials using Anamorelin, but subjective outcomes and lean body mass, which appear to have consistently improved in our study and others, may be more productive. Further studies are needed to identify the ideal objective way to measure activity in patients with cancer.

Patients with significant fatigue, cachexia and inflammation such as those selected by our eligibility criteria

tend to be very ill advanced cancer patients who often deteriorate rapidly due to disease progression. This explains why the dropout rate was elevated (38%) in our study. The level of attrition we observed is consistent with other fatigue and cachexia symptom trials conducted in the advanced cancer population by our team and others [13, 37, 38]. However, there is a critical need for effective symptom management interventions in this target population, particularly for symptoms like fatigue and cachexia that are highly distressing, as improved treatment modalities could significantly benefit these patients. Thus, new strategies to better manage dropouts in clinical studies targeting advanced cancer patients are of fundamental importance.

The study has several limitations. We found significant improvement in PROMIS-F, and MFSI-SF (general) but not in the other fatigue scales. Similarly there was improvement in the Godin leisure test scores but no improvement in the mean daytime activity scores assessed using actigraphy. The possible explanations for these varying findings might be the relatively small sample size as well as the possibility that this intervention helps more subjective fatigue than mean day time activity. Further well powered randomized controlled studies are needed to confirm the findings and to understand the mechanisms associated with CRF improvement using correlative studies such as pro-inflammatory cytokine analysis, as the subjects were adherent to the study interventions [39]. The lack of control or placebo arm is a major limitation. The contribution of the placebo effect to efficacy could not be directly quantified [40]. Also, the fatigue improvement in some scales could have been due to PA, nutrition counseling, Anamorelin, combination of these interventions, or just improvements with time from treatment. Further placebo-controlled studies are needed. The relatively lower levels of adherence to the actual PA prescription, and dietary recommendations despite high levels of adherence to PA and nutrition counseling sessions suggests that further research is necessary to determine the optimal PA and dietary prescription, and the possible need for booster counseling sessions to strengthen the potential of Anamorelin to improve fatigue and cachexia outcomes. We designed this exploratory study to evaluate the patients who completed the primary outcome at Day 43. This might be a limitation and future research should address intention treat analysis, perhaps looking at additional ways to dramatically reduce the number of dropouts. One potential strategy might be to consider patients at a much earlier stage of disease with signs of early cachexia.

Together, our study results are reassuring in that the combination of Anamorelin with a manualized physical activity intervention and nutritional counseling was tolerable and support the preliminary efficacy of this combination in improving not just CRF but also anorexia and body composition measures.

Conclusion

The use of the combination therapy was associated with improvement of patient reported subjective outcomes for CRF, activity, anorexia, body composition, and IGF-1 levels. There was no significant improvement in the physical performance outcomes and mean daytime activity. Future randomized controlled trials of the combination therapy for CRF are justified.

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Author contribution Dr Sriram Yennurajalingam had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Yennurajalingam, Hui, Bruera. Acquisition, analysis, or interpretation of data: Yennurajalingam, Basen-Engquist, Reuben, Fellman, Shete, Maddi, Williams, Dev, Hui, and Bruera. Drafting of the manuscript: Yennurajalingam, Basen-Engquist, Reuben, Fellman, Shete, Maddi, Williams, Dev, Hui, and Bruera Critical revision of the manuscript for important intellectual content: Yennurajalingam, Basen-Engquist, Reuben, Fellman, Shete, Maddi, Williams, Dev, Hui, and Bruera. Statistical analysis: Fellman, Shete, Maddi, Williams. Administrative, technical, or material support: Yennurajalingam, Bruera. Supervision: Yennurajalingam, Bruera.

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Availability of data and material The data presented in this study are available on request from the corresponding author. The data are not publicly available due to investigational treatment.

Code availability Available on request from the corresponding author.

Declarations

Ethics approval and consent to participate The University of Texas MD Anderson Cancer Center Institutional Review Board approved the protocol. Informed consent was obtained from all subjects involved in the study.

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