

A multi-targeted treatment approach to cancer cachexia: Auckland's Cancer Cachexia evaluating Resistance Training (ACCeRT) trial

Elaine S. Rogers^{1,2*}, Rita Sasidharan², Graeme M. Sequeira³, Matthew R. Wood⁴, Stephen P. Bird⁵, Justin W.L. Keogh⁶, Bruce Arroll¹, Joanna Stewart⁷ & Roderick D. MacLeod⁸

¹Department of General Practice and Primary Health Care, University of Auckland, ²Department of Medical Oncology, Auckland City Hospital, Auckland, New Zealand, ³School of Sport, Manukau Institute of Technology, Auckland, New Zealand, ⁴Sports Performance Research Institute NZ, AUT University, Auckland, New Zealand, ⁵Department of Medical and Exercise Science, University of Wollongong, Wollongong, New South Wales, Australia, ⁶Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia, ⁷Department of Epidemiology and Biostatistics, University of Auckland, Auckland, New Zealand, ⁸Northern Clinical School, University of Sydney, Sydney, New South Wales, Australia

Abstract

Background Cancer cachexia is a condition often seen at diagnosis, throughout anti-cancer treatments and in end-stage nonsmall-cell lung cancer patients.

Methods and results Participants with late-stage non-small-cell lung cancer and cachexia (defined as $\geq 5\%$ weight loss within 12 months) were randomly assigned 1:2 to 2.09 g of eicosapentaenoic acid (EPA) and 300 mg of cyclo-oxygenase-2 inhibitor celecoxib orally once daily vs. same dosing of EPA, celecoxib, plus two sessions per week of progressive resistance training and 20 g of oral essential amino acids high in leucine in a split dose over 3 days, after each session. Primary endpoint was the acceptability of the earlier multi-targeted approach. Main secondary endpoints included change in body weight and fat-free mass, by bioelectric impedance analysis and total quadriceps muscle volume by magnetic resonance imaging over 20 weeks. Sixty-nine patients were screened resulting in 20 patients being enrolled. Acceptability scored high, with 4.5/5 (Arm A) and 5/5 (Arm B) for EPA and 5/5 for celecoxib within both arms and 4.8/5 for progressive resistance training sessions and 4.5/5 for essential amino acids within Arm B, all at Week 20. Results showed a net gain in bioelectric impedance analysis fat-free mass of +1.3 kg, $n = 2$ (Arm A), compared with +0.7 kg, $n = 7$ (Arm B) at Week 12, and -1.5 kg, $n = 2$ (Arm A), compared with -1.7 kg, $n = 4$ (Arm B) at Week 20. Trends in efficacy in terms of improvement and/or stability in cachexia markers were seen within magnetic resonance imaging muscle volume, albumin, and C-reactive protein levels within both arms. There were no exercise-related adverse events, with one possible related adverse event of asymptomatic atrial fibrillation in one participant within Arm A.

Conclusions Non-small-cell lung cancer cachectic patients are willing to be enrolled onto a multi-targeted treatment regimen and may benefit from cachexia symptom management even during the late/refractory stage.

Keywords Cancer cachexia; EPA; COX-2; PRT; EAA

Received: 26 December 2018; Accepted: 5 March 2019

*Correspondence to: Dr Elaine S. Rogers, Department of General Practice and Primary Health Care, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. Email: es.rogers@auckland.ac.nz

Introduction

The most widely used definition for cancer cachexia found is 'a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment'.¹ Over the last few decades, a number of pharmacological agents and methods of support have been investigated to address the primary areas of cancer cachexia,^{2,3} either by monotherapy or by combinations of agents.^{4–6} Recent publications have shown progress in a number of areas including the ghrelin receptor agonist anamorelin, which possesses both anabolic and appetite-stimulating properties, as per ROMANA 1, 2, and 3 studies,^{7,8} the novel non-selective beta-blocker with central 5-HT_{1a} and partial β_2 receptor agonist espidolol, which possesses both anabolic and anti-catabolic properties, as per ACT-ONE study,⁹ and the anabolic properties of testosterone.¹⁰

During this time, there has been a change in the consideration of cachexia from a 'very late change' and inescapable event to 'an early phenomenon' with signs of cachexia present upon primary cancer diagnosis even if weight loss has not yet occurred. This has led to the recent shift in developing effective treatments aimed at preventing rather than reversing the symptoms, as seen in the earlier studies.^{7–10}

This is in contrast to results of earlier clinical cachexia studies where anti-cancer treatment was not permitted and recruited from end-stage cancer populations, which showed efficacy with significant improvements in cachexia endpoints including bone-free arm muscle mass and body weight,¹¹ physical functioning and weight (gastrointestinal group),¹² and increase in body weight and handgrip, with decreased C-reactive protein (CRP) levels,¹³ all in placebo-controlled, randomized studies in late-stage refractory cancer cachexia. Completion rates have also been shown to be similar within these earlier studies, ranging from 43% ($n = 50$)¹¹ to 60% ($n = 200$)¹⁴ at 8 weeks.

Current published literature in palliative care includes an open-label study of twice weekly exercise in palliative patients for 6 weeks. Results showed efficacy and safety within this end-stage cancer population.¹⁵ A recent systematic review and meta-analysis of 66 high-quality exercise in cancer studies supported emerging evidence and the many benefits of exercise at various time points within the cancer journey.¹⁶ Views of palliative care patients and their relatives regarding participating within a palliative care research study have recently been reviewed.¹⁷ Eight studies were identified, with common themes including a desire to retain autonomy, altruism, and the potential for personal gain by participating in a research study, and patients were generally happy to participate and did want research studies to be offered and discussed.¹⁷

Recent knowledge gained around the loss of skeletal muscle mass being the main component of cancer cachexia has led to the need to measure and quantify skeletal muscle, in terms of stabilization or increase/loss in both skeletal muscle mass/volume and strength.² Muscle strength and function can be inferred from the analysis of muscle volume, and measuring this over time is important in assessing changes during ageing, training, and disease processes. The current 'gold standard' of measuring muscle volume involves utilizing contiguous transverse magnetic resonance imaging (MRI) scans.¹⁸ Additional benefits of MRI analysis include the analysis of both muscle volume and anatomical cross-sectional area, along with morphological features and distribution, and can characterize the loss of muscle quality, for example, intramuscular fat infiltration, fibrous connective tissue, and oedema.¹⁹ This is becoming important as loss of mobility has been shown to be related to muscle strength and increased muscle lipid content, which can be quantified by both MRI and magnetic resonance spectroscopy.¹⁹

In theory, an effective treatment for cancer cachexia may require a multi-targeted approach. The combination of the anti-cachectic agent eicosapentaenoic acid (EPA) and the cyclo-oxygenase-2 (COX-2) inhibitor celecoxib has been previously tested in a small study in non-small-cell lung cancer (NSCLC) patients with some benefit.¹³ Similarly, the use of progressive resistance training (PRT) and/or the oral ingestion of essential amino acids (EAA) has been reported to provide a potent anabolic stimulus on skeletal muscle and appears acceptable in older adults and other cancer groups.^{20,21}

The study combination was chosen to target and decrease the pro-inflammatory cytokines by using a COX-2 inhibitor (celecoxib) and EPA and increase muscle anabolism with PRT and EAA high in leucine post-exercise, with the overall goal of stabilizing the effect of muscle catabolism/anabolism to a potential net gain in overall muscle mass. It was decided to improve body composition analysis within this study in terms of utilizing 3T MRI scanner data and to use the analysis of muscle volume to represent muscle strength and function.¹⁸ This analysis was to be combined with a formal assessment of leg strength testing, which has been utilized within exercise studies within various cancer populations.^{22,23}

Materials and methods

Study design

Auckland's Cancer Cachexia evaluating Resistance Training (ACCeRT) study is a single-centre, open-label, prospective, randomized controlled feasibility study. All participants provided written informed consent. The study protocol was approved by Northern Y Ethics Committee, Hamilton, New Zealand (NTY/11/06/064), and complied with the

International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice Guidelines, and the Declaration of Helsinki. Study protocol has been published²⁴ and registered with Australian New Zealand Clinical Trials Registry. Eligible patients were at least 18 years of age; had histologically confirmed NSCLC; had cachexia as per Evans *et al.*²⁵ (defined as involuntary weight loss of $\geq 5\%$ within the previous 12 months or body mass index < 20 kg/m²); and had three of the following: decreased muscle strength, fatigue, anorexia, low fat-free mass (FFM), and abnormal biochemistry [CRP > 5 mg/L, interleukin (IL)-6 > 4 pg/mL, haemoglobin < 12 g/dL, and hypoalbuminaemia < 3.2 g/dL]. Eligible participants had been assessed, and no further treatment was available to them indicating end-stage refractory cachexia. Participants were required to have a life expectancy of at least 4 months. Exclusion criteria included the use of appetite stimulants (medroxyprogesterone acetate, megestrol acetate, 4 mg o.d. of dexamethasone, or 30 mg o.d. of prednisolone), pleural effusion that causes greater than or equal to CTC grade 2 dyspnoea, or an abnormal baseline 12-lead electrocardiogram.

Randomization and masking

Participants were randomly assigned (1:2) to Arm A; EPA and COX-2 inhibitor (celecoxib) or Arm B; and EPA, COX-2 inhibitor (celecoxib), PRT, and EAA by a randomization table created by computerized sequence generation. Enclosed treatment assignments were serially numbered in opaque, sealed envelopes and opened sequentially after the participant's name and other details had been written on the appropriate envelope.²⁶ The ACCeRT study was open label, and all participants were aware of the allocated treatments. Research staff assessing MRI analysis were masked to the participants' assigned intervention group throughout the analysis.

Procedures

All participants received orally 5.5 mL (2.09 g) of EPA plus 300 mg celecoxib o.d. mane, with participants allocated to Arm B receiving two PRT sessions per week (Tuesdays and Fridays), followed by 20 g of EAA high in leucine in split dose over the following 3 days. Study period of 20 weeks, with all participants having the opportunity to continue and/or receive study medication/training sessions under compassionate use. These results will be published separately. Participants could withdraw at any time or at the discretion of the investigator because of further progression of their disease. Dose reductions or interruptions of EPA, celecoxib, PRT, and EAA were permitted.

Acceptability was assessed by the analysis of a patient-rated Likert-scored questionnaire asking 10 questions on the acceptability of the earlier multi-targeted approach (Supporting Information, *Figure S1*). Both groups were asked five core questions around the acceptability/palatability of taking the EPA and celecoxib daily and if they wish to continue with this medication. Participants allocated to Arm A were asked one further question to determine if they would like to commence the PRT sessions and EAA. Participants allocated to Arm B were asked further four questions on the acceptability/palatability of participating in the PRT sessions and taking the EAA and if they wish to continue with this component of the study. Likert scores had a range of 1 for 'strongly disagree' to 5 for 'strongly agree'; therefore, the higher the score representing, the higher the acceptability of the study medication and/or programme. Body composition (FFM, total body weight, and fat mass) was measured by bioelectrical impedance analysis (BIA) (Tanita). 3T MRI total quadriceps muscle volume was assessed by the University of Auckland Centre for Advanced Magnetic Resonance Imaging. Handgrip strength (HGS) was assessed by handgrip dynamometry of the dominant hand using the average of three attempts with 1 min rest between attempts (Jamar[®] or TTM Smedlays). Leg strength was measured by the use of a customized rig attached to a load cell to determine isometric force, with maximum voluntary contraction assessed over a period of 10 s with considerable verbal encouragement by the clinical exercise physiologist. Contractions were repeated three times at 1 min intervals. Symptom burden was measured with the anorexia-cachexia scale (ACS) and physical well-being scale (PWB) from the Functional Assessment of Anorexia/Cancer Therapy (FAACT, Version 4). Fatigue was measured by the Multidimensional Fatigue Symptom Inventory—Short Form (MFSI-SF) and overall quality of life by World Health Organization Quality of Life—Abbreviated (WHOQOL-BREF). The FAACT-ACS is scored ranging from 0 to 48, and FAACT-PWB is scored ranging from 0 to 28, with higher scores showing lower symptom burden, and the MFSI-SF 30-item ranging from -24 to 96 with higher scores indicating increased fatigue. Pro-inflammatory cytokine analysis (IL-1 β , IL-6, and tumour necrosis factor- α) by Luminex MAGPIX[®]. Both albumin and CRP levels were analysed and then incorporated into the Glasgow prognostic score (GPS). Compliance results were analysed as percentage attendance of the total study sessions and percentage taken of the total study medication. All earlier data were collected at baseline, Weeks 3, 6, 9, 12, 16, and 20, except for MRI data at screening visit and last visit or Week 20/end of trial visit only. Study participants were followed up for overall survival.

Treatment-emergent adverse events with an onset date on or after the date of the first drug dose and including up to 4 weeks after last drug dose were graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 3.0).

Endpoints

The primary endpoint was the acceptability of a multi-targeted approach of supportive care in cachectic NSCLC participants. Secondary endpoints were the change from baseline over 20 weeks in body composition by BIA, 3T MRI total quadriceps muscle volume, HGS and leg strength, FAACT-ACS, FAACT-PWB, MFSI-SF, WHOQOL-BREF, pro-inflammatory cytokines (IL-1 β , IL-6, and tumour necrosis factor- α), albumin, CRP and corresponding GPS, and overall survival.

Statistical analysis

Analyses of primary and secondary endpoints were based on the full analysis set defined according to the intent-to-treat principle. Safety analysis was performed for the safety analysis population. Full analysis set consists of all participants who were randomized with a valid post-baseline assessment. Following the intent-to-treat principle, participants were analysed according to the treatment they were assigned to at randomization. Safety analysis population consisted of all participants who received at least one dose of any of the study drugs/intervention. Participants were analysed according to the treatment received. Trends in efficacy and safety of the earlier multi-targeted approach of supportive care in cachectic NSCLC participants were examined. These results will then be used to determine the most appropriate outcome measures to power a future study.

Results

From April 2012 until end of May 2015 (38 months), 69 patients were screened resulting in 20 patients being included, (Figure 1 trial profile). Recruitment rate (screened vs. consented) was 30.4% (21/69), and randomization rate of 28.9% (20/69) was due to one participant consented but died before randomization. This rate is higher than the recently published phase II multimodal intervention study, PREMENAC²⁷ with a recruitment rate of 11.5%, however lower than the recruitment rates of 86% within both ROMANA 1 and 2 studies.⁷ Approximately a third declined to participate 31.9% (22/69), and a further third were excluded 33.3% (23/69). The two main reasons for patients not being eligible were decreased Eastern Cooperative Oncology Group—Performance Status 8.7% (6/69) and either renal and/or cardiac co-morbidities 5.8% (4/69). The attrition rate of those recruited was 35% (7/20) at Week 6, 55% (11/20) at Week 12, and 70% (14/20) at Week 20. All participants completing the 20 week study continued with compassionate use of study medication and PRT sessions.

The analysis was based on 7 and 13 participants randomly assigned to Arm A and Arm B, respectively. The baseline characteristics are shown in Table 1. Groups were well matched with respect to gender and ethnicity, with 13 male (65%), 7 female (35%), and 3 Māori (15%) participants reflecting the current population experiencing NSCLC in New Zealand in terms of gender and ethnicity.²⁸ Overall, the mean and range of baseline characteristics were similar in both groups, except for the following: participants within Arm B entered the study

Figure 1 Trial profile for Auckland's Cancer Cachexia evaluating Resistance Training.

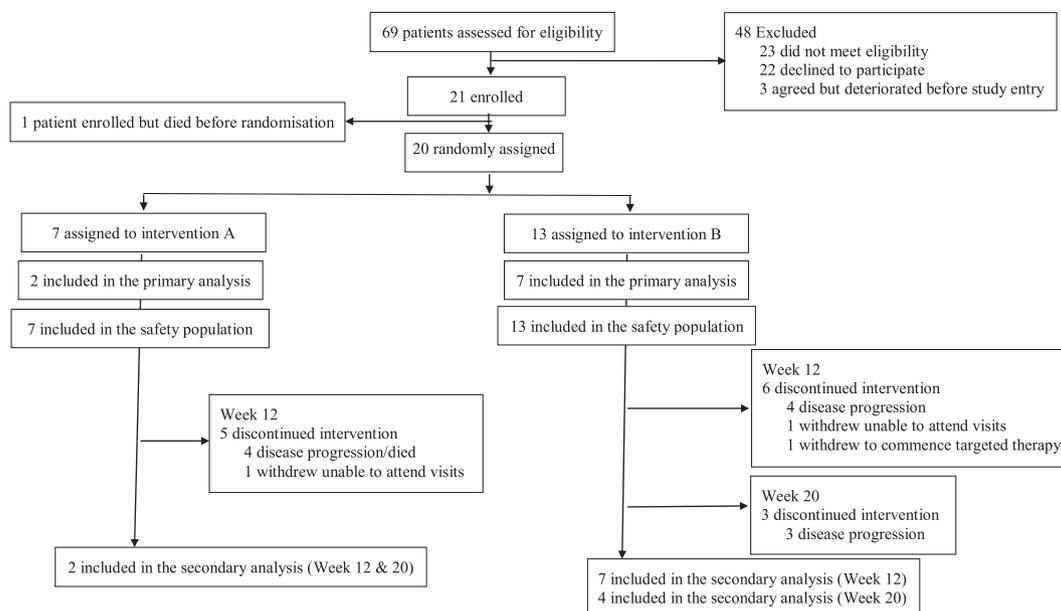


Table 1 ACCeRT baseline characteristics

	Total <i>n</i> = 20	Arm A <i>n</i> = 7	Arm B <i>n</i> = 13
Age (years)	68.2 (42–87)	72.7 (64–81)	65.8 (42–87)
Race			
European	15 (75%)	5 (33%)	10 (67%)
Māori	3 (15%)	1 (33%)	2 (67%)
Asian	1 (5%)	1	0
Filipino	1 (5%)	0	1
Gender			
Male	13 (65%)	5 (38%)	8 (62%)
Female	7 (35%)	2 (29%)	5 (71%)
Body weight (kg)			
All	62.9 (42.2–89.0)	64.7 (45.6–89.0)	61.9 (42.2–79.0)
Male	67.9 (45.6–89.0)	67.6 (45.6–89.0)	68.0 (49.9–79.0)
Female	53.6 (42.2–78.6)	57.6 (52.7–62.4)	52.0 (42.2–78.6)
Weight loss at entry (%)	–8.0 (–5.0 to –20.2)	–7.1 (–5.6 to –9.8)	–8.4 (–5.0 to –20.2)
5–10	16 (80%)	6 (38%)	10 (62%)
10–15	0	0	0
>15	1 (5%)	0	1
Low BMI	3 (15%)	1 (33%)	2 (67%)
Weight loss (days)	83 (10–296)	117 (31–296)	64 (10–115)
Time since diagnosis (days)	603 (125–1328)	723 (140–1328)	538 (125–1181)
Diagnosis NSCLC			
Adenocarcinoma	14 (70%)	4 (29%)	10 (71%)
Squamous	6 (30%)	3 (50%)	3 (50%)
Albumin (g/L)	37 (25–43)	37 (34–43)	37 (25–42)
CRP (mg/L)	71 (3–322)	97 (8–322)	57 (3–164)
GPS	1.1 (0–2)	1 (0–2)	1.2 (0–2)
Lines of previous treatment			
Total (excluding surgery)	2 (1–5)	1.6 (1–3)	2.2 (1–5)
Surgery	2	0	2
Targeted therapy (gefitinib/erlotinib)	11	3	8
Clinical study	4	1	3

ACCeRT, Auckland's Cancer Cachexia evaluating Resistance Training; BMI, body mass index; CRP, C-reactive protein; GPS, Glasgow prognostic score; NSCLC, non-small-cell lung cancer.

Data are mean (range) or *n* (%).

with a higher weight loss with one participant experiencing severe weight loss greater than 15%, lower body weight, and reduced time from diagnosis and had received a higher number of lines of anti-cancer treatments. This suggests that this group was experiencing progression of their advanced cancer in a shorter time period.

Main baseline secondary outcomes for participants not completing to Week 12 due to further disease progression or death (*n* = 8/11) were compared with participants completing to Week 12 (Supporting Information, Table S1). Three participants were well but withdrew from the study and not included in this analysis. The results indicate that these participants had on average lower body composition and strength values from BIA, MRI, and HGS data and higher levels of anorexia/cachexia symptoms and fatigue, lower albumin levels, and higher CRP levels resulting in a higher GPS. Acknowledging that this is a small group of data, it can be utilized to generate possible ranges for exclusion criteria for future refractory cachexia studies.

The acceptability questionnaire was completed at a number of study time points. Results are presented at Week 12 and Week 20/end of trial visit. All participants randomized to Arm B completed the acceptability questionnaire at either

the planned study visit or the last visit due to participant's preference or study team withdrawal. Unfortunately, only three out of the seven participants randomized to Arm A completed the questionnaire.

Acceptability and compliance data are shown in Tables 2–4. At Week 12, only two participants in Arm A completed the questionnaire for EPA acceptability, both scoring 5 and one participant scoring 5 for celecoxib. In Arm B, six participants completed the questionnaire for EPA acceptability with mean score of 3.8, and seven participants completed the questionnaire for celecoxib with mean score of 3.7, PRT mean score of 4.6, and EAA mean score of 3.9. At Week 20, two participants in Arm A had EPA acceptability mean score of 4.5 and one participant again scoring 5 for celecoxib. In Arm B, three participants completed the questionnaire for EPA acceptability all scoring 5, with all four participants scoring 5 for celecoxib and a mean score of 4.8 for PRT and 4.5 for EAA.

Compliance (deemed as >50% for each participant) was 100% (9/9) at Week 12 and 83.3% (5/6) at Week 20 for EPA, 88.9% (8/9) at Week 12 and 83.3% (5/6) at Week 20 for celecoxib, 100% (7/7) at Week 12 and 100% (4/4) at Week 20 for the PRT component, and 71.4% (5/7) at Week 12 and 75% (3/4) at Week 20 for EAA. One arm B participant pre-

Table 2 Acceptability questionnaire results

	Arm A		Arm B	
	Week 12	Week 20	Week 12	Week 20
EPA acceptable (5)	5	4.5	3.8	5
Celebrex acceptable (5)	5	5	3.7	5
Commencing PRT and medication (5)	5	5		
PRT acceptable (5)			4.6	4.8
EAA acceptable (5)			3.9	4.5
Continue with exercise and medication (5)			3.9	4.5

EAA, essential amino acids; EPA, eicosapentaenoic acid; PRT, progressive resistance training.

Data are mean. The highest score available for each question is within parentheses.

study entry was experiencing intermittent diarrhoea related to previously participating in the clinical REVEL study. Data from this study showed toxicity (any grade) of 32% of diarrhoea and 16% mucosal inflammation.²⁹ The decision was made to stop all study medication at Week 6 and to continue only with the PRT sessions for this arm B participant. There was no change in the frequency of diarrhoea, and it was never resolved and was still experienced intermittently until the participant's death. One arm A participant was taking diclofenac 100 mg sustained release for bilateral hip osteoarthritis pre-study entry. This medication was stopped and switched to the study medication of celecoxib 300 mg o.d. The participant found the switch unacceptable and stopped the celecoxib and returned to diclofenac at Week 5. Two arm B participants found all the medication overwhelming and had EAA dose reduction to 6 g per session (12 capsules over the 3 days). One participant had 83 and 80% PRT

Table 3 Compliance table for individual participants by trial arm completing Week 12

	Percentage taken of the total study dose per session				
	EPA	Celecoxib	PRT	EAA	Overall
Arm A	100	36.9 ^a			68.5
Arm A	98.8	98.8			98.9
Mean	99.4	67.9			83.7
Arm B	100	85.7 ^a	87.5	18.8 ^b	73
Arm B	86.9 ^c	86.9 ^c	75 ^c	69.6 ^c	79.6
Arm B	50 ^a	50 ^a	91.7	54.2 ^a	61
Arm B	100	100	100	94.6	98.7
Arm B	100	100	95.8	91.6	96.9
Arm B	78.6 ^a	100	83	15.4 ^b	69.3
Arm B	100	100	100	99	99.8
Mean	87.9	88.9	90.4	63.3	82.6

EAA, essential amino acids; EPA, eicosapentaenoic acid; PRT, progressive resistance training.

Twelve weeks equals 84 doses of EPA and celecoxib, 24 PRT sessions, and 400 g of EAA.

^aStudy medication stopped.

^bPlanned dose reduction.

^cStopped intermittently because of radiotherapy-induced nausea and vomiting.

Table 4 Compliance table for individual participants by trial arm completing Week 20

	Percentage taken of the total study dose per session				
	EPA	Celecoxib	PRT	EAA	Overall
Arm A	100	22.1 ^a			61.1
Arm A	99.2	99.2			99.2
Mean	99.6	60.7			80.2
Arm B	100	100	100	96.4	99.1
Arm B	100	100	97.5	95	98.1
Arm B	47.1 ^a	100	80	15.3 ^b	60.6
Arm B	100	100	100	99.4	99.9
Mean	86.8	100	94.4	76.5	89.4

EAA, essential amino acids; EPA, eicosapentaenoic acid; PRT, progressive resistance training.

Twenty weeks equals 140 doses of EPA and celecoxib, 40 PRT sessions, and 800 g of EAA.

^aStudy medication stopped.

^bPlanned dose reduction.

attendance at Weeks 12 and 20, respectively. This participant was the youngest in age to be enrolled onto the study and was the main caregiver for young children and found it difficult at times to attend for family reasons. All other participants had family members who were willing to bring them to the twice weekly sessions. Interestingly, both participants from Arm A scored 5 'strongly agree' in wishing to commence the PRT sessions and EAA. The earlier results conclude that on average, the administration of EPA, celecoxib, PRT, and EAA at this dose and frequency was acceptable in this population.

Secondary endpoints

Weight, FFM, MRI total quadriceps muscle volume, albumin, CRP, and GPS per trial arm are shown in *Tables 5 and 6*. Participants in Arm A had a mean increase in body weight by +0.7 kg, whereas those in Arm B lost -0.8 kg at Week 12; however, both arms had mean weight loss of -2 and -3.7 kg, respectively, at Week 20. *Figure 2A and 2B* shows percentage change in weight for each participant by trial arm. *Figure 2A* depicts percentage change in total body weight data from baseline to Week 12. Data show one net gain and one stable value within arm A participants compared with two net gains and one stable and four net losses within arm B participants. This indicates the reversal and stability of weight loss within some participants at Week 12. *Figure 2B* depicts percentage change in total body weight data from baseline to Week 20. Data show two net losses within arm A participants compared with one net gain and three net losses within arm B participants. This indicates the reversal of weight loss within one arm B participant at Week 20. Total body weight results indicate, on average, a net gain in weight at Week 12 and then weight loss returned within Arm A. For arm B participants completing Week 12, weight loss returned at Week 9 onwards, while for arm B participants completing

Table 5 Data for main secondary outcomes for participants by trial arm completing to Week 12

		Arm A (n = 2)	Arm B (n = 7)
Weight (kg)	Baseline	79.9	64.6
	12 weeks	80.6	63.8
	Difference	+0.7	-0.8
	% difference	+0.9	-2.2
FFM (kg)	Baseline	58.9	48.6
	12 weeks	60.2	49.3
	Difference	+1.3	+0.7
	% difference	+2.3	+0.3
MRI total quadriceps muscle volume (cm ³)	Baseline		
	12 weeks		
	Difference		
	% difference		
Male (n = 0/n = 1)	Baseline		798
	12 weeks		627
	Difference		171
	% difference		-21.4%
Female (n = 0/n = 1)	Baseline		673
	12 weeks		620
	Difference		53
	% difference		-7.9%
Albumin (g/L)	Baseline	39.0	38.4
	12 weeks	35.0	35.7
	Difference	-4.0	-2.7
	% difference	-11.2	-6.5
CRP (mg/L)	Baseline	35.5	33.9
	12 weeks	95	54.0
	Difference	+59.5	+20.1
	% difference	+442.7	+61.2
GPS (0-2)	Baseline	0.5	1.0
	12 weeks	1.5	1.1
	Difference	+1	+0.14
	% difference	+100	0

CRP, C-reactive protein; FFM, fat-free mass; GPS, Glasgow prognostic score; MRI, magnetic resonance imaging. Data are mean.

Week 20, weight loss was delayed and returned at Week 16 onwards (Supporting Information, *Figures S2 and S3*).

In terms of FFM, participants in both Arm A and Arm B gained +1.3 and +0.7 kg at Week 12, followed by FFM loss of -1.5 and -1.7 kg, respectively, at Week 20. *Figure 3A and 3B* shows percentage change in FFM for each participant by trial arm. *Figure 3A* depicts percentage change in FFM from baseline to Week 12. Data show one net gain and one stable value within arm A participants compared with three net gains and one stable and three net losses within arm B participants. *Figure 3B* depicts percentage change in FFM from baseline to Week 20. Data show two net loss values within arm A participants compared with one net gain and three net losses within arm B participants. These results indicate that within Arm A, there was an increase in FFM in the context of increasing weight at Week 12. While there was

Table 6 Data for main secondary outcomes for participants by trial arm completing to Week 20

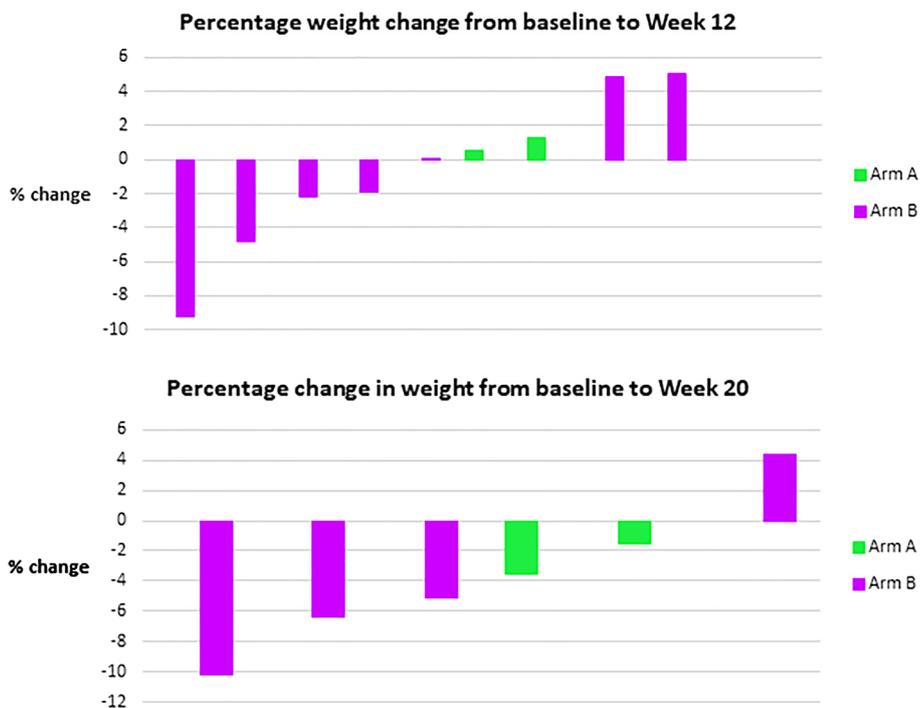
		Arm A (n = 2)	Arm B (n = 4)
Weight (kg)	Baseline	79.9	69.2
	20 weeks	78.0	65.6
	Difference	-2	-3.7
	% difference	-2.6	-4.3
FFM (kg)	Baseline	58.9	51.2
	20 weeks	57.4	49.5
	Difference	-1.5	-1.7
	% difference	-2.6	-2.9
MRI total quadriceps muscle volume (cm ³)	Baseline	1093	1024
	20 weeks	1208	973
	Difference	+115	-51
	% difference	+12.5	-3.0
Male (n = 2/n = 2)	Baseline	1093	1281
	20 weeks	1208	1145
	Difference	+115	-137
	% difference	+12.5	-10.2
Female (n = 0/n = 2)	Baseline		769
	20 weeks		801
	Difference		+33
	% difference		+4.2
Albumin (g/L)	Baseline	39.0	36.8
	20 weeks	37.5	33.5
	Difference	-1.5	-3.3
	% difference	-3.5	-7.2
CRP (mg/L)	Baseline	35.5	39.0
	20 weeks	65.0	97.0
	Difference	+29.5	+58.0
	% difference	+61.8	+128.5
GPS (0-2)	Baseline	0.5	1.0
	20 weeks	1.0	1.3
	Difference	+0.5	+0.3
	% difference	+50	+25

CRP, C-reactive protein; FFM, fat-free mass; GPS, Glasgow prognostic score; MRI, magnetic resonance imaging. Data are mean.

an increase in FFM within Arm B, this occurred in the context of stable and/or decreasing total body weight. Interestingly, for arm B participants completing Week 20 while the total body weight was stable, the FFM was increasing up to Week 12, which could be attributed to the addition of PRT sessions and/or EAA and the potential stimulation of the anabolic pathway.

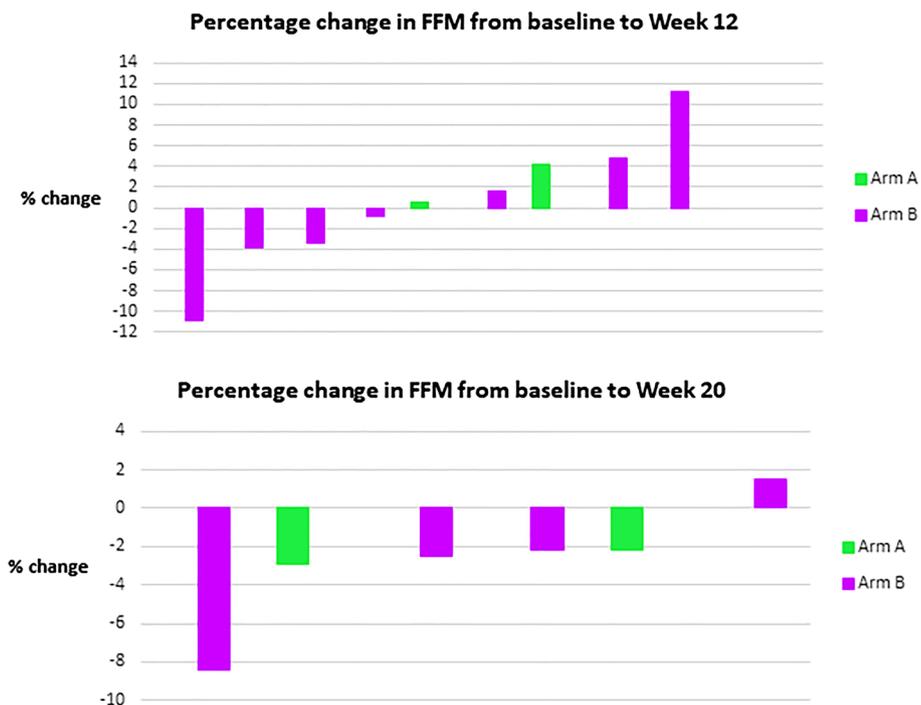
Data from *Table 6* show the mean MRI total quadriceps muscle volume change from baseline to Week 20 of +12.5% (+4.3 and +20.7%) within Arm A, compared with -3% (range -18.3 to +4.8%, n = 4) within Arm B. One arm A participant underwent the MRI scan, but unfortunately, the images were unable to be analysed as standardized for all the other images due to the significant deficiency of adipose tissue. There was no objective difference in the signal intensities between the muscle and the surrounding tissue, resulting in an inability

Figure 2 (A) Waterfall plot of percentage weight change for each participant by trial arm from baseline to Week 12. (B) Waterfall plot of percentage weight change for each participant by trial arm from baseline to Week 20.



to automatically segment and therefore assess the volume as per the study protocol. An adjustment in the degree of fat saturation at the time of acquisition may have been beneficial; however, this was probably unlikely because of the

Figure 3 (A) Waterfall plot of percentage fat-free mass (FFM) change for each participant by trial arm from baseline to Week 12. (B) Waterfall plot of percentage FFM change for each participant by trial arm from baseline to Week 20.



deficiency of adiposity. This corresponded with BIA data of 1.1 kg of fat mass (2.5%) at the screening visit. Because of attrition of participants as discussed earlier, pre-treatment and post-treatment scan data were only available for two participants allocated to Arm A and eight allocated to Arm B (two at Week 9, data not shown). *Figure 4* depicts percentage change in MRI muscle volume from baseline to Week 20 for each participant by trial arm. Data show two net gains within both arm A participants compared with two net gain and two net losses within arm B participants. These results indicate, on average, a net gain of total quadriceps muscle volume for participants within Arm A, compared with a slight net loss within Arm B. If taking the predefined definition of response as per study by Greig *et al.*,³⁰ individual data within Arm A show two major responders with the net change of +4.3 and +20.7%, both over 20 weeks. Within Arm B, there was one major and one minor responder with a net change of +4.8 and +3.6% respectively, and two non-responders with -2 and -18.3% over 20 weeks. Both arm A participants experienced weight loss over the longest time period and were maybe at an earlier stage in the refractory cachexia period. However, these results suggest that the use of EPA and celecoxib could potentially preserve muscle volume during this early refractory cachexia stage.

Notable differences in both the albumin and CRP levels show reduced albumin loss and lower CRP levels in Arm B when compared with Arm A, -11.2 vs. -6.5% change in albumin levels and +442.7 vs. +61.2% in CRP levels in Arms A and B, respectively, at Week 12. This was reflected with the corresponding GPS at Week 12 (+100 vs. +0%). One arm A participant received antibiotics and low-dose prednisone for a pulmonary/upper respiratory infection around Week 12, which resulted in improved levels of albumin and CRP levels after this study visit. The trend of CRP levels within Arm B indicates that the levels of inflammation were reduced and on average lower than Arm A until Week 12 (Supporting Information, *Figures S4* and *S5*), and then levels start to increase at Week 20, and maybe attributed to the PRT sessions and study medication allocated to Arm B. Data show that the

combination of EPA and celecoxib was not adequate in reducing or maintaining reduced CRP levels in many of the participants throughout the 20 week study. Over the 20 week period, the mean albumin levels changed from 39 to 37.5 g/L within Arm A and 36.8 to 33.5 g/L within Arm B and minimal change in corresponding GPS; these changes were small over this period within a refractory cachexia population, suggesting a possible positive effect on inflammation and nutrition within both study treatment arms or that the GPS was not sensitive to identify further progression in a refractory cachexia population.

Regarding the leg strength data, there were a number of issues regarding the robustness of the equipment and the lack of any form of calibration for potential drift over time. Therefore, the results of the isometric leg strength testing were taken with some trepidation and not reported. This was further supported by lack of trend and random aberrant results seen in the later participants who were assessed three and four times weekly. However, it can be concluded that all participants were happy to undergo this testing.

High adherence rates and high scores on the primary endpoint acceptable questionnaire showed that the participants found engaging in the PRT sessions is acceptable. At each session, participants were assessed, and the exercise programme was adapted. It was decided to format the reporting of the PRT sessions in terms of the planned training programme and if the participants at each phase of the programme under-achieved, achieved, or over-achieved as per *Table 7*. This would allow the assessment of the planned programme in terms of achievability in this population, along with gaining data on potentially increasing the programme in terms of sessions. Results show that all participants achieved the planned regimen and Borg rating of perceived exertion 11 'light' at the end of Phase I/Week 4, except for one who had a historical neck, bilateral hips, and lower spine injury from a childhood road traffic accident; the programme was modified to include a slower progression through the intensity levels across the programme phases and under-achieved at each phase. *Table 8* shows results for Phase III/

Figure 4 Waterfall plot of percentage magnetic resonance imaging (MRI) muscle volume change for each participant by trial arm from baseline to Week 20.

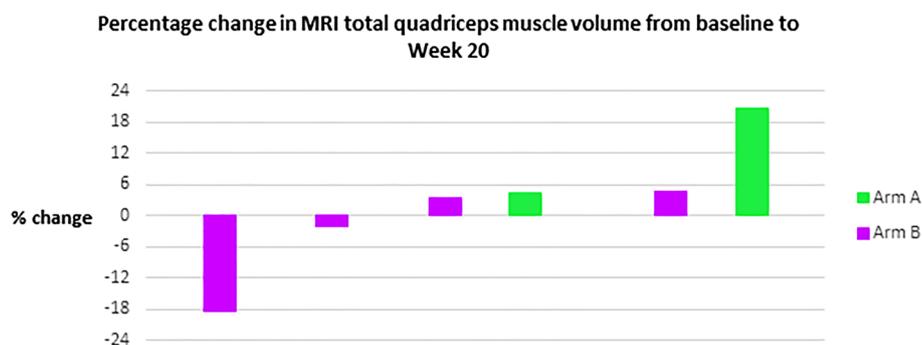


Table 7 Planned progression from baseline to Week 20

	Phase I Weeks 1–4 PRT 1–8	Phase II Weeks 5–8 PRT 9–16	Phase III Weeks 9–12 PRT 17–24	Phase IV Weeks 13–16 PRT 25–32	Phase V Weeks 17–20 PRT 33–40
Planned	'Very light' to 'light' Borg RPE 8–11	'Somewhat hard' Borg RPE 12–13		'Hard' Borg RPE 14–15	

PRT, progressive resistance training; RPE, rating of perceived exertion.

Week 12 with three participants under-achieved, three participants achieved, and one participant over-achieved. Results for Phase V/Week 20 showed two participants under-achieved and two participants achieved as per *Table 9*. These results show a number of events. First, that 92% ($n = 11/12$) of participants with various entry levels of fitness and weight loss managed to achieve the planned programme within Phase I/Week 4. Second, that the earlier low volume, low-intensity training progressing to a moderate volume, moderate- to high-intensity training programme was both acceptable and safe within an NSCLC end-stage cachectic population.

Small differences were seen within arms for the following secondary outcomes: HGS, pro-inflammatory cytokines, FAACT-ACS, FAACT-PWB, MFSI-SF, and WHOQOL-BREF at both Weeks 12 and 20 (Supporting Information, *Tables S2* and *S3*), indicating either stability or testing unable to detect large differences within a refractory cachexia population.

The median survival within Arm A was Week 16 ($n = 3/7$, 43%) and Week 20 ($n = 6/13$, 46%) within Arm B, as shown in *Figure 5*. There were 35 adverse events in all participants. *Table 10* shows treatment-related adverse events of Grades 1–2 and Grades 3 and 4 by trial arm. The most common treatment-related adverse events were musculoskeletal ($n = 4/7$, 57%) and dyspnoea ($n = 2/7$, 29%) within Arm A and both infection and bone pain ($n = 3/13$, 23%) within Arm B, all at Grade 3. There were no exercise-related events and no treatment-related deaths. There was one possible case of study medication that induced atrial fibrillation (AF) within one arm A participant at Week 12. The participant was asymptomatic and did not require hospital admission, and it was decided to continue with the study medication under regular surveillance, as it was possible that this symptom was related

to his underlying condition of progressing NSCLC. AF is often seen in the older population,³¹ and chronic pulmonary disease has also been shown to be a factor.³² Post-operative thoracic surgery is the most frequent form of cancer-related AF, and there has been the suggestion that the inflammatory complication of cancer is represented by AF.³² All the earlier factors were seen within this participant. Interestingly, 35% ($n = 7/20$) of participants were already receiving a cardiac medication at baseline.

Discussion

This study demonstrates that the two interventions assessed in this study were both feasible and have a high acceptability in patients with NSCLC. The multimodal intervention utilized within Arm B was safe without any exercise-induced adverse events. We observed that both interventions resulted in the stabilization of total body weight and FFM loss at Week 12 (defined as $\pm 2\%$), with ongoing body weight loss returning at Week 16 and FFM loss returning at Week 20 within both arms. However, these findings must be interpreted with caution as the trial was not powered to examine differences between arms, along with study attrition especially seen within Arm A.

A multimodal intervention approach has been recommended during many reviews, and a multimodal study similar to the ACCeRT study has recently been published.²⁷ Main differences between the studies are seen in the study population, with the ACCeRT study targeting end-stage refractory cachexia, while the Pre-MENAC study targets the prevention of cancer cachexia, that is, pre-cachexia/cachexia. Pre-MENAC study is a randomized phase II feasibility trial of lung and pancreatic cancer patients undergoing Cycles III and IV of

Table 8 Lower and upper body Borg RPE for each individual arm B participant completing to Week 12

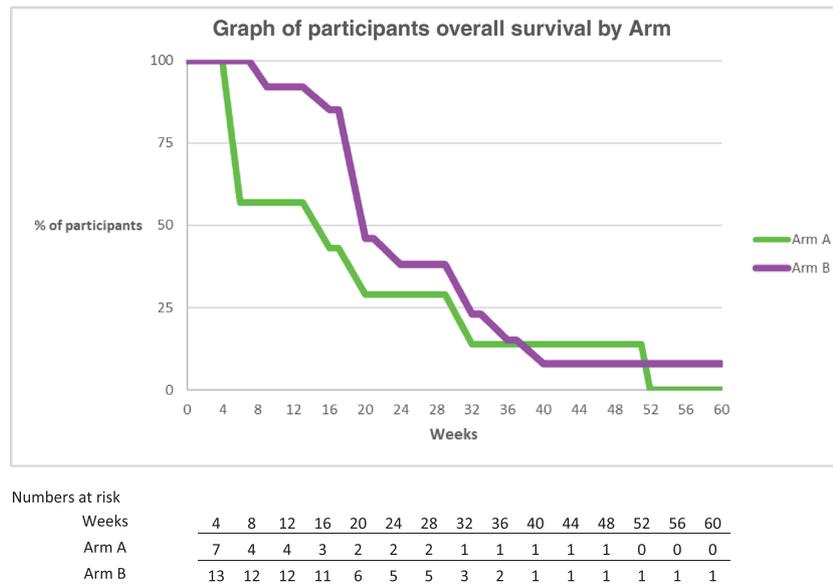
	Lower		Upper	
	Baseline	Week 12	Baseline	Week 12
Arm B	11	11	11	11
Arm B	11	13	11	13
Arm B	11	11	11	11
Arm B	11	15	11	15
Arm B	11	13	11	13
Arm B	9	11	9	11
Arm B	11	13	11	13
Mean	10.7	12.4	10.7	12.4

RPE, rating of perceived exertion.

Table 9 Lower and upper body Borg RPE for each individual arm B participant completing to Week 20

	Lower		Upper	
	Baseline	Week 20	Baseline	Week 20
Arm B	11	13	11	13
Arm B	11	15	11	15
Arm B	9	11	9	11
Arm B	11	15	11	15
Mean	10.5	13.5	10.5	13.5

RPE, rating of perceived exertion.

Figure 5 Overall survival by trial arm from study entry.

standard chemotherapy, randomized to standard care or oral nutritional supplements, anti-inflammatory (celecoxib) and home-based aerobic (twice weekly) and resistance training (three times weekly). Pre-MENAC study results show a mean +0.91 kg weight gain in the treatment arm compared with a mean -2.12 kg loss within the control arm at Week 6.²⁷ This was similar to Week 6 ACCeRT data (not shown) of weight gain of +0.9 kg (Arm A) and slight loss of -0.7 kg (Arm B). This is in contrast to the results of another pre-cachexia/cachexia population study investigating anamorelin within the ROMANA 1 and 2 studies. Results showed a mean weight gain +2.2 kg in the treatment arm compared with +0.14 kg in the placebo arm (ROMANA 1) and +0.95 kg in the treatment arm compared with -0.57 kg in the placebo arm (ROMANA 2), all at 12 weeks,⁷ with +3.1 kg in the treatment arm compared with +0.9 kg in the placebo arm at 24 weeks (ROMANA 3).⁸

Optimum endpoint for cancer cachexia studies is currently being investigated. At the time of designing the ACCeRT study, change in total body weight, FFM/LBM by either BIA, dual-energy X-ray absorptiometry (DEXA), or later lumbar-3 computed tomography analysis was just beginning, along with measure of physical function. It was decided by the ACCeRT study team to utilize 3T MRI total quadriceps volume data, along with leg strength analysis to strengthen these potential important endpoints. Unfortunately, as discussed earlier, the leg strength data measured by isometric load cell have been taken with some trepidation. Participants in general complied well with the isometric leg strength testing device. This assessment was objective, and once limitations are corrected and formalized will provide valuable data around physical function for future studies.

ACCeRT is the first study to utilize 3T MRI data within a cancer cachexia study and has shown that even during the refractory cachexia period, it is possible to promote anabolism with the net gain within muscle mass, as seen within both participants within Arm A and both female participants within Arm B, all at Week 20.

ACCeRT is also the first study to investigate the use of exercise as part of a multimodal regimen in a refractory cachexia population. Interestingly, compliance for attendance for the exercise sessions was higher than in previous published studies in the adjuvant cancer setting. The START study investigated exercise three times a week concurrently with adjuvant chemotherapy for breast cancer, and results showed the attendance rates of 72% (aerobic) and 68.2% (resistance) over 18 weeks,³³ compared with ACCeRT attendance of 95.1% for 36 sessions/18 weeks, in this end-stage population. Attendance rates were compared with previously discussed Pre-MENAC study of 60% of the population attending >50% for both resistance and aerobic over 6 weeks.²⁷ With the study design of 1:1 session with a clinical exercise physiologist, the attendance rates are true and did not rely on patient's data through self-reported logs. Acceptability as defined as a score of 4 or 5 on the questionnaire showed that both EPA and celecoxib had the highest score, followed by the PRT component and then EAA.

The ACCeRT study has a number of limitations. First is the attrition rate within both arms, especially within Arm A, which resulted in only 57% ($n = 4/7$) completing Week 3 and then 28.5% ($n = 2/7$) completing from Weeks 6 to 20. This decreased the data gained within this study arm. Second, the study participants all had experienced $\geq 5\%$ weight loss, and all but one had evidence of their NSCLC disease further

Table 10 Serious adverse events by trial arm

	Arm A			Arm B		
	Grade			Grade		
	1–2	3	4	1–2	3	4
Cardiac						
Hypotension				1 (8%)		
Gastrointestinal						
Dehydration	1 (14%)					
Diarrhoea	1 (14%)					
Obstruction			1 (8%)			
Infection	1 (14%)		1 (8%)	3 (23%)		
Metabolic						
Hyperbilirubinaemia					1 (8%)	
Hypercalcaemia				1 (8%)		
Hyponatraemia				1 (8%)		
Musculoskeletal						
Other	4 (57%)					
Neurology						
Cranial CNVII				1 (8%)		
Confusion	1 (14%)		1 (14%)	1 (8%)		
Motor					1 (8%)	
Pain						
Bone		1 (14%)			3 (23%)	
Tumour	1 (14%)					1 (8%)
Pulmonary/upper respiratory						
Dyspnoea		2 (29%)		1 (8%)		
Pleural effusion	2 (29%)	1 (14%)				
Renal						
Incontinence—urinary				1 (8%)		
Vascular						
Thrombosis					1 (8%)	
Total	4	11	1	5	12	2

Data are *n* (%). All treatment-emergent events displayed are defined as adverse events beginning on or after first dose and through the 28 day post-dose window.

progressing indicating refractory cachexia. Therefore, these results are restricted to patients experiencing NSCLC and refractory cachexia, and generalizability to other tumour groups and pre-cachexia/cachexia population cannot be made. Third, it must be acknowledged that the lack of a placebo arm and open-label design and missing values increases the risk of bias of these results. Future studies could possibly contain a placebo arm and where possible blinded allocation; this could be in the form of a placebo vs. celecoxib, an isocaloric, isonitrogenous oral supplement vs. EPA and simple gentle stretching exercises that do not stimulate anabolic pathways vs. PRT. Regarding possible contamination of Arm A undergoing uncontrolled exercising, both participants were

questioned weekly around this. With the plethora of literature and recommended guidelines around the benefits of physical exercise within all stages of the cancer journey,^{34–36} it would be difficult to repeat this study or use a design of a non-exercise arm in future studies. Fourth, the ACCeRT study utilized BIA for body composition changes instead of DEXA or lumbar-3 computed tomography data. BIA method can underestimate the FFM compared with DEXA or computed tomography analyses in oncological patients because of fluid shifts.¹⁹ However, because the participants did not show any signs of oedema, ascites, or dehydration, underestimation is likely to be a minor issue. Fifth, the expense of the 3T MRI acquisition scans and the staff to perform the analysis is not always possible at all research/clinical centres. Sixth is the analysis of ‘classic cachexia’ pro-inflammatory cytokines instead of analysing the newer biomarkers, for example, myostatin, activin A, insulin-like growth factor-1, leptin, and zinc-alpha-2-glycoprotein, which would have determined if a true anabolic and a reduction of the catabolic effect was seen.

In conclusion, ACCeRT is the first study to utilize a multi-targeted regimen in the refractory cancer population, and a comparison with other research studies cannot be made at this point. It has been stated that the combination of physical inactivity, inflammation, and poor nutritional status may prevent the reversal of weight and muscle loss and that any intervention would be unlikely to see a reversal of the cachexia-related symptoms within the last 90 days of life.³⁷ The ACCeRT study results indicate that patients are willing to be enrolled onto a multi-targeted treatment regimen and may benefit from cachexia symptom management even during the late/refractory stage.

The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle — Rapid Communications (von Haehling S, Ebner N, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle — Rapid Communications. *J Cachexia Sarcopenia Muscle Rapid Communications* 2017; 1:e44:1–2.)

Funding

The authors are grateful to Pfizer Australia and New Zealand for the donated celecoxib (Celebrex[®]), Metagenics (Aust) Pty Ltd for the donated EPA (Ethical Nutrients Hi-Strength Liquid Fish Oil), and Musashi (Notting Hill, Australia) for the donated essential amino acids, along with the University of Auckland and the Louisa and Patrick Emmet Murphy Foundation, managed by the Public Trust (New Zealand), for their generous grants to accomplish this clinical study.

Author contributions

E.S.R. conceived the study. E.S.R., R.D.M., and J.W.L.K. participated in the design of the study. J.S. was responsible for the statistical planning of the trial. E.S.R. and R.D.M. wrote the study protocol. R.S. provided the study medical assistance. G.M.S. and M.R.W. provided the progressive resistance programme development. S.P.B. provided the nutritional advice. B.A. provided the study oversight. All authors read and approved the final manuscript.

Acknowledgements

We wish to thank all the participants for participating in the ACCeRT study.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Acceptability questionnaire

Figure S2. Weight change over time for participants completing to week 12

Figure S3. Weight change over time for participants

completing to week 20

Figure S4. CRP level change over time for participants completing to week 12

Figure S5. CRP level change over time for participants completing to week 20

Table S1. Comparison data for main secondary outcomes for participants not completing or completing to week 12

Table S2. Data for other secondary outcomes for participants by trial arm completing to week 12

Table S3. Data for other secondary outcomes for participants by trial arm completing to week 20

Conflict of interest

S.P.B. is a consultant to Musashi, Vitaco Health Australia Pty Ltd. All other authors declare that they have no competing interests.

The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle – Rapid Communications* (von Haehling S, Ebner N, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle – Rapid Communications. *JCSM Rapid Commun* 2018; 1:e44:1-2.)

References

1. Fearon KCH, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;**12**:489–495.
2. Muscaritoli M, Bossola M, Aversa Z, Bellantone R, Rossi-Fanelli F. Prevention and treatment of cancer cachexia: new insights into an old problem. *Eur J Cancer* 2006;**42**:31–41.
3. von Haehling S, Anker SD. Treatment of cachexia: an overview of recent developments. *J Am Med Dir Assoc* 2014;**15**:866–872.
4. Mantovani G, Macciò A, Madeddu C, Gramignano G, Serpe R, Massa E, et al. Randomised phase III clinical trial of five different arms of treatment for patients with cancer cachexia: interim results. *Nutrition* 2008;**24**:305–313.
5. Mantovani G, Macciò A, Madeddu C, Serpe R, Massa E, Dessi M, et al. Randomised phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncologist* 2010;**15**:200–211.
6. Mantovani G, Macciò A, Madeddu C, Gramignano G, Lusso MR, Serpe R, et al. A phase II study with antioxidants, both in the diet and supplemented, pharmaconutritional support, progestagen, and anti-cyclooxygenase-2 showing efficacy and safety in patients with cancer-related anorexia/cachexia and oxidative stress. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:1030–1034.
7. Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol* 2016;**17**:519–531.
8. Currow D, Temel JS, Abernethy A, Milanowski J, Friend J, Fearon KCH. ROMANA 3: a phase 3 safety extension study of anamorelin in advanced non-small cell lung cancer (NSCLC) patients with cachexia. *Ann Oncol* 2017;**28**:1949–1956.
9. Stewart Coats AJ, Ho GF, Prabhaskar K, von Haehling S, Tilson J, Brown R, et al. Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomised, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). *J Cachexia Sarcopenia Muscle* 2016;**7**:355–365.
10. Wright TJ, Dillon EL, Durham WJ, Chamberlain A, Randolph KM, Danesi C, et al. A randomised trial of adjunct testosterone for cancer-related muscle loss in men and women. *J Cachexia Sarcopenia Muscle* 2018;**9**:482–496.
11. Gordon JN, Trebble TM, Ellis RD, Duncan HD, Johns T, Goggin PM. Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005;**54**:540–545.
12. Fearon KCH, Barber MD, Moses AG, Ahmedzai SH, Taylor GS, Tisdale MJ, et al. Double-blind, placebo-controlled, randomised study of eicosapentaenoic acid diester in patients with cancer cachexia. *J Clin Oncol* 2006;**24**:3401–3407.
13. Cerchiatti LCA, Navigante AH, Castro MA. Effects of eicosapentaenoic and docosahexaenoic n-3 fatty acids from fish oil and preferential Cox-2 inhibition on systemic syndromes in patients with advanced lung cancer. *Nutr Cancer* 2007;**59**:14–20.
14. Fearon KCH, von Meyenfeldt MF, Moses AGW, van Geenen R, Roy A, Gouma DJ, et al. Effect of a protein and energy dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer

- cachexia: a randomised double blind trial. *Gut* 2003;**52**:1479–1486.
15. Oldervoll LM, Loge JH, Paltiel H, Asp MB, Vidvei U, Wiken AN, et al. The effect of a physical exercise program in palliative care: a phase II study. *J Pain Symptom Manage* 2006;**31**:421–430.
 16. Speck RM, Courneya KS, Mâsse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* 2010;**4**:87–100.
 17. White CD, Hardy JR. What do palliative care patients and their relatives think about research in palliative care?—a systematic review. *Support Care Cancer* 2010;**18**:905–911.
 18. Hudelmaier M, Wirth W, Himmer M, Ring-Dimitriou S, Sanger A, Eckstein F. Effect of exercise intervention on thigh muscle volume and anatomical cross-sectional areas—quantitative assessment using MRI. *Magn Reson Med* 2010;**64**:1713–1720.
 19. Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: current concepts and imaging implications. *AJR Am J Roentgenol* 2015;**205**:W255–W266.
 20. Drummond MJ, Dreyer HC, Fry CS, Glynn EL, Rasmussen BB. Nutritional and contractile regulation of human skeletal muscle protein synthesis and mTORC1 signalling. *J Appl Physiol* 2009;**106**:1374–1384.
 21. Madeddu C, Macciò A, Astara G, Massa E, Dessì M, Antoni G, et al. Open phase II study on efficacy and safety of an oral amino acid functional cluster supplementation in cancer cachexia. *Med J Nutrition Metab* 2010;**3**:165–172.
 22. Battaglini C, Bottaro M, Dennehy C, Rae L, Shields E, Kirk D, et al. The effects of an individualised exercise intervention on body composition in breast cancer patients undergoing treatment. *Sao Paulo Med J* 2007;**125**:22–28.
 23. Adamsen L, Quist M, Andersen C, Møller T, Herrstedt J, Kronborg D, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. *BMJ* 2009;**339**:b3410.
 24. Rogers ES, MacLeod RD, Stewart J, Bird SP, Keogh JWL. A randomised feasibility study of EPA and Cox-2 inhibitor (Celebrex) versus EPA, Cox-2 inhibitor (Celebrex), Resistance Training followed by ingestion of essential amino acids high in leucine in NSCLC cachectic patients—ACCeRT study. *BMC Cancer* 2011;**11**:493.
 25. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. *Clin Nutr* 2008;**27**:793–799.
 26. Schulz KF. Subverting randomisation in controlled trials. *JAMA* 1995;**274**:1456–1458.
 27. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomised phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2017;**8**:778–788.
 28. Ministry of Health 2012, Selected cancers 2013, 2014, 2015 [Available from: www.health.govt.nz/publication/selected-cancers-2012-2013-2014.]
 29. Garon EB, Ciuleanu T-E, Arrieta O, Prabhaskar K, Syrigos KN, Goksel T, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *The Lancet* 2014;**384**:665–673.
 30. Greig CA, Johns N, Grey C, MacDonald A, Stephens NA, Skipworth RJE, et al. Phase I/II trial of formoterol fumarate combined with megestrol acetate in cachectic patients with advanced malignancy. *Support Care Cancer* 2014;**22**:1269–1275.
 31. Sankaranarayanan R, Kirkwood G, Dibb K, Garratt CJ. Comparison of atrial fibrillation in the young versus that in the elderly: a review. *Cardiol Res Pract* 2013(Article ID 976976):<https://doi.org/10.1155/2013/976976>.
 32. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: Atrial fibrillation in cancer. *J Am Coll Cardiol* 2014;**63**:945–953.
 33. Courneya KS, Segal RJ, McKenzie DC, Dong H, Gelmon K, Friedenreich CM, et al. Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. *Med Sci Sports Exerc* 2014;**46**:1744–1751.
 34. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010;**42**:1409–1426.
 35. Segal R, Zwaal C, Green E, Tomasone JR, Loblaw A, Petrella T, et al. Exercise for people with cancer: a clinical practice guideline. *Curr Oncol* 2017;**24**:40–46.
 36. Stefani L, Galanti G, Klika R. Clinical implementation of exercise guidelines for cancer patients: adaptation of ACSM's guidelines to the Italian model. *J Funct Morphol Kinesiol* 2017;**2**:4.
 37. Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, et al. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? *Am J Clin Nutr* 2013;**98**:1012–1019.