Original Article

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Acceptability, Compliance, and Safety of Non-small Cell Lung Cancer Cachectic Participants Continuing Compassionate Access in the ACCeRT Clinical Study

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Abstract:

Objective: Cancer cachexia is defined as: a 'multifactorial syndrome', and it has been suggested that a multitargeted approach is required in its management. High prevalence is seen within non-small cell lung cancer, and patients may continue to experience cachexia post end of anti-cancer treatment, and in the late/end stage.

Material and Methods: Participants who had completed week 20/End of Trial visit in the main Auckland's Cancer Cachexia evaluating Resistance Training (ACCeRT) study were invited to continue with treatment under compassionate use. Participants could continue with 2.09 g of eicosapentaenoic acid (EPA), 300 mg COX-2 inhibitor (celecoxib), once daily; plus two sessions per week of progressive resistance training (PRT), and 20 g oral essential amino acids (EAA); high in leucine, in a split dose over three days post each session. Data was collected on the acceptability, compliance and adherence to medication/PRT sessions. Secondary endpoints included: change in body weight and fat free mass,

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handgrip and leg strength, the Functional Assessment of Anorexia/Cachexia Therapy, Multidimensional Fatigue Symptom Inventory-Short Form, World Health Organization Quality of Life — BREF, Glasgow prognostic score, and pro-inflammatory cytokines.

Results: All six participants, who completed the main ACCeRT study, opted to continue with compassionate use. Acceptability remained high, with overall compliance to last study/PRT visit of 81.0% for EPA, 98.8% for celecoxib, 78.9% for PRT and 77.2% for EAA. Participants continued to lose body weight and Fat-Free Mass, along with reduced albumin and increased C-Reactive protein levels. Mean time on compassionate study treatment was 78 days, and with a mean overall survival of 257 days (140 + 117).

Conclusion: Non-small cell lung cancer (NSCLC) cachectic patients are willing to be enrolled onto a multi-targeted treatment regimen, and may benefit from cachexia symptom management even during their late/refractory stage.

Keywords: Refractory cancer cachexia, Resistance Training, NSCLC cachectic patients, multi-targeted treatment

Introduction

Cachexia still remains a challenge within the oncology population. A recent, cross-sectional study investigated the prevalence of cancer cachexia in 386, of 426 eligible patients attending selected hospitals within Norway.[1] Prevalence of 21.0% was seen amongst outpatients; increasing to 51.0% within the inpatient population. High levels were again reported within the lung cancer population, with 36.0% amongst outpatients and increasing to 83.0% of inpatients. Patients were asked if they required either decreased or increased attention to their weight. Fifteen percent of outpatients and 20.0% of inpatients requested: "more or a lot more focus", on this condition.[1]

It has long been established that cachectic cancer patients have been associated and/or documented to have lower response rates to traditional chemotherapy as well as shorter median survival,[2] which has been attributed to a number of factors. Firstly, because chemotherapy dosage is based on body surface area, thinner patients receive a lower dose of chemotherapy. Secondly, treatment breaks, due to chemotherapy toxicities, are higher in this population of patients.[3] Thirdly, previous chemotherapy treatments and concurrent multi-modality treatments e.g., surgery and radiotherapy will also affect nutritional status, which further confound the condition. A retrospective review suggested that metastatic melanoma patients treated with chemotherapy, immunotherapy and targeted therapy with a body mass index (BMI) of either overweight or obese, as classified by the World Health Organisation (WHO), had improved progression-free survival and overall survival when compared with patients of normal weight.[4] Improved survival within early obese cancer patients has been termed as the: 'obesity paradox'[5], and has been shown in a number of different cancers.[6] Failure to respond to pembrolizumab has been recently identified, due to elevated protein catabolism and clearance seen within cancer cachectic patients.[7,8] With the increase in the use of immune checkpoint inhibitors that have revolutionized the current treatments in oncology, this highlights the need to diagnose and support cachectic patients throughout their anti-cancer treatments and beyond.

Cancer cachexia has recently been defined as multifactorial; including, elements of decreased total body weight, adjoined with skeletal muscle loss contributing to impaired function, respiratory complications and fatigue, decreased food intake, metabolic changes, increased inflammation and catabolism; affecting the patients' overall quality of life.[9,10]

Multi-targeted/multi-modal studies have been designed to address these factors, and recently the results of the Pre-Multimodal Exercise/Nutrition/Anti-inflammatory Treatment for Cachexia (Pre-MENAC) study have been published. This study investigated the use of standard cancer care versus a multi-modal regimen, comprising of a single baseline session of nutritional counselling (approximately 30 minutes), eicosapentaenoic acid (EPA) via two 220 mL cartons of oral nutritional supplement (Prosure © Abbott) equaling a net intake of 2 g/day, 300 mg celecoxib OD, twice weekly home-based aerobic sessions (approximately 30 minutes) and thrice weekly resistance training of six individualized exercises (approximately 20 minutes). The study period of six weeks ran concurrently, with cycles I and II of chemotherapy in non-small cell lung cancer (NSCLC), and pancreatic cancer patients with less than 20.0% weight loss over the preceding six months.[11] This study recruited pre-cachexia/cachexia patients, with the results demonstrating no significant difference between groups on muscle mass, as assessed by computerized tomography (CT) derived measures, or physical activity assessed by 6MWT and ActivPAL. Compliance rates of 60.0% for exercise, 48.0% for nutritional supplement and 76.0% for celecoxib were observed.[11]

Anamorelin is the only registered drug for the treatment of cancer cachexia recently approved by Japan in December 2020.[12] The intervention(s) being tested within the ACCeRT study are an alternative treatment regimen.

The study was designed to address cachectic factors within a multi-targeted regimen, within end-stage/refractory cachectic NSCLC patients.[13] The study combination was chosen to increase muscle anabolism, using progressive resistance training (PRT) and essential amino acids (EAA) high in leucine, post exercise as well as to target and decrease the proinflammatory cytokines by using a cyclooxygenase-2 inhibitor (celecoxib) and EPA. Results from the main study showed high acceptability, and compliance rates of 86.8% for EPA, 100.0% for celecoxib, 94.4% for PRT/exercise, and 76.5% for EAA within the treatment group at week 20. Trends in efficacy, in terms of improvement and/or stability in cachexia markers, were seen within magnetic resonance imaging (MRI) muscle volume, albumin, and C-reactive protein (CRP) levels within both arms.[14] Participants who had completed the ACCeRT main study could continue with medication and/or exercise sessions post end of the main study under compassionate use (CU). Data on the ongoing acceptability, compliance and safety of this multi-targeted regimen in refractory cachectic NSCLC patients will be used to calculate the power and number of participants required for a future phase II study.

Material and Methods

Northern Y Ethics Committee, Hamilton, New Zealand (NTY/11/06/064) approved the published study protocol.[13] The study was registered with the Australian and New Zealand Clinical Trials Registry, and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice Guidelines, and the Declaration of Helsinki. Participants consisted of those whom had completed week 20/End of Trial (EOT) visit in the main ACCeRT study, had maintained an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤2, and for which the investigator considered suitable to continue to receive additional treatments and exercise sessions. Participants were permitted to withdraw at any time, or at the discretion of the investigator; due to further progression of their disease.

Procedures

All participants could choose to continue to orally receive 2.09 g of EPA, plus 300 mg of celecoxib once daily. Arm A participants could choose to commence with the addition of two PRT sessions per week (Tuesdays and Fridays), followed by 20 g EAA high in leucine in split

doses over the following three days. Arm B participants could choose to continue with PRT/EAA. Dose reductions or interruptions of all study medications, and exercise sessions were permitted. The intention of compassionate PRT differed depending on study randomisation to either Arm A or Arm B within the main study. Those participants that had completed the 20-week PRT programme (Arm B) had the option to continue with resistance training. The intention for this group of participants was to maintain the same training intensity and volume achieved at week 20/EOT of the PRT programme. Those participants that were not allocated to the PRT exercise group (Arm A) had the option of starting the PRT programme, using the same exercise programme designed from the main study. All participants were medically assessed every four weeks.

Outcomes

Data was collected on the acceptability of a multi-targeted regimen of supportive care in cachectic NSCLC participants continuing with compassionate use. Acceptability was assessed by the analysis of a patient rated Likert scored questionnaire, asking 10 questions on the acceptability of the above multi-targeted approach. Likert scores had a range of five, five being: 'strongly agree', and one being: 'strongly disagree', with higher scores representing higher acceptability of the study medication and/or exercise programme. Secondary endpoints were continued over from the main study, and included the change from baseline in body composition (fat-free mass (FFM), total body weight, and fat mass), as measured by Bioelectrical Impedance Analysis (BIA) (Tanita), muscle strength (hand grip dynamometry and isometric knee extension, measured by the use of a customised rig attached to a load cell). Symptom burden was measured with the anorexia-cachexia scale and physical well-being scale from the Functional Assessment of Anorexia/Cancer Therapy (version 4). Fatigue was measured by The Multidimensional Fatigue Symptom Inventory-Short Form, and overall quality of life by WHOQOL-BREF. Proinflammatory cytokine analysis (IL-1β, IL-6, and TNF-α) was measured by Luminex MAGPIX®. Albumin and CRP levels were incorporated into the Glasgow Prognostic Score. Compliance results were analysed as percentage of the total study medication, and percentage of attendance of the total study PRT sessions. All the above data were collected every four weeks, and study participants were followed up for overall survival

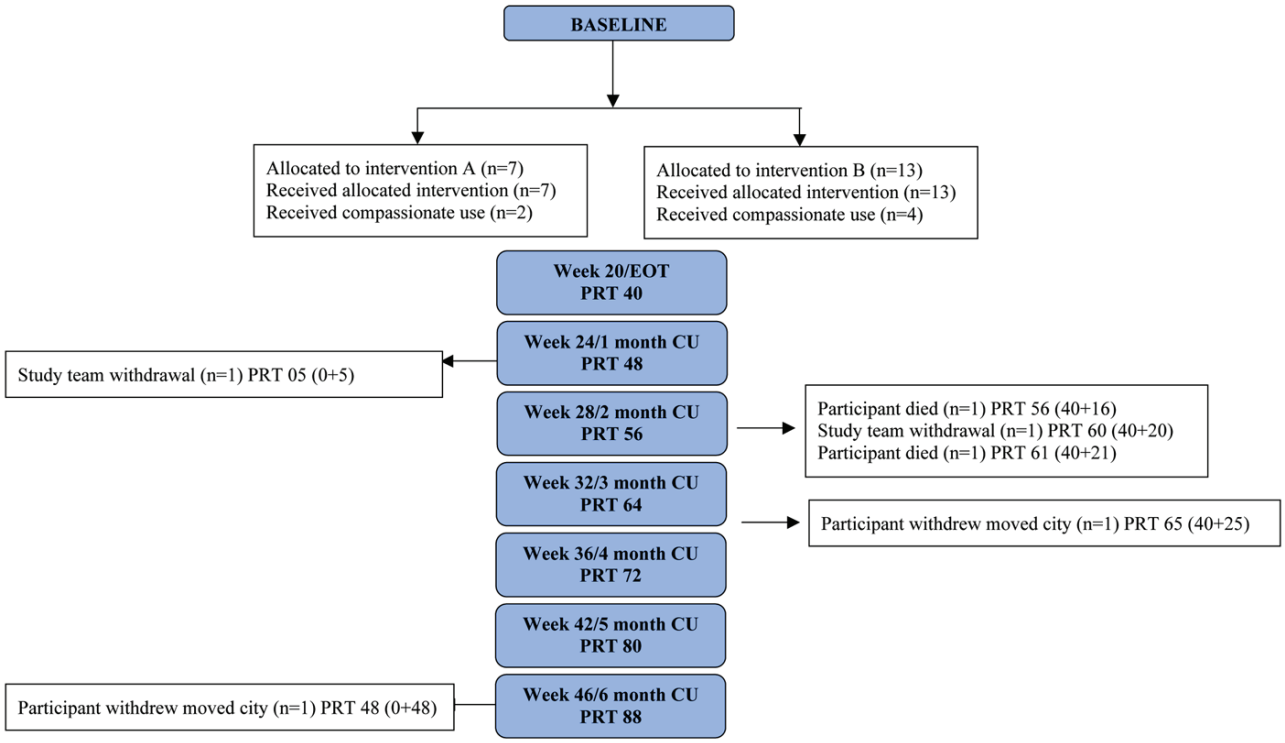
Results

Sixty-nine patients were screened, resulting in 20 patients being enrolled onto the main study (Figure 1 – Consolidated Standards of Reporting Trials profile). All six participants, completing week 20/EOT visit from the main study continued with study medication, and either continued/began PRT sessions and EAA under CU (two allocated to Arm A, and four allocated to Arm B). Baseline characteristic data is shown in Table 1.

The acceptability questionnaire was completed at each monthly CU visit, as shown in Table 2. Results showed high mean acceptability scores of 4 to 5 for EPA, celecoxib, PRT and EAA, and commitment to continue with the regimen from CU 1 through to CU 5 visit.

Compliance data is shown in Table 3 (deemed as >50.0% for each participant) and was 80.0% (n=4/5) for EPA, 100.0% (n=5/5) for celecoxib, 83.3% (n=5/6) for the PRT component, and 75.0% (n=3/4) for EAA.

Overall compliance was 81.0% for EPA, 98.8% for celecoxib, 78.9% for PRT, and 77.2% for EAA; as shown in Table 4. These results conclude that on average, the administration of EPA, celecoxib, PRT and EAA at this dose and frequency was acceptable within this population; with three of the six participants continuing with all four elements of the multi-targeted regimen.



PRT=progressive resistance training, CU=compassionate use, EOT=end of trial

Figure 1 Consolidated Standards of Reporting Trials

Table 1 Auckland's Cancer Cachexia evaluating Resistance Training compassionate use Baseline data/characteristics

	Total Mean (range) n=6	
	At ACCeRT entry	**At ACCeRT CU entry**
Age (years)	63.7 (42 to 71)	
Race		
European	4	
Māori	2	
Gender		
Male	4	
Female	2	
Weight loss (%)		
All	−7.9 (−5.0 to −9.8)[a]	−3.7 (−10.2 to +4.4)[b]
0.0 to 5.0%	0	2
5.0 to 10.0%	5	3
+0.0 to +5.0%	0	1
Low BMI	1[a]	0

Table 1 (Continued)

	Total Mean (range) n=6	
	At ACCeRT entry	**At ACCeRT CU entry**
Body weight (kg)		
All	72.8 (45.1 to 89.1)[c]	69.7 (47.1 to 87.7)[d]
Male	78.3 (70.7 to 89.1)[c]	74.1 (66.7 to 87.7)[d]
Female	61.9 (45.1, 78.6)[c]	60.9 (47.1, 74.6)[d]
Time since diagnosis (days)	429 (125 to 920)[e]	
Diagnosis NSCLC		
Adenocarcinoma	4	
Squamous	2	
Albumin (g/L)	37.5 (25 to 44)[c]	34.8 (27 to 40)[d]
CRP (mg/L)	37.8 (5 to 62)[c]	86.3 (2 to 211)[d]
GPS	0.8 (0 to 2)[c]	1.2 (0 to 2)[d]

[a]Weight loss defined as percentage weight loss at main ACCeRT study entry. *one participant study entry with low BMI.

[b]Weight loss/gain defined as weight change from Random visit to week 20/EOT visit of main ACCeRT study.

[c]Data at study Random visit.

[d]Data at week 20/EOT visit/start of CU.

[e]Time since diagnosis defined as histology date to date of main ACCeRT study entry.

CU=compassionate use, BMI=body mass index, NSCLC=non-small cell lung cancer, CRP=C-reactive protein, GPS=glasgow prognostic score, EOT=end of trial, ACCeRT=Auckland's Cancer Cachexia evaluating Resistance Training

Table 2 Acceptability questionnaire results

	CU 1	**CU 2**	**CU 3**	**CU 4**	**CU 5**
EPA acceptable (5)	5[a]	5[a]			
Celebrex acceptable (5)	5[b]	5[b]	4.5[a]	5[c]	5[c]
PRT acceptable (5)	5[b]	5[b]	4.5[a]	5[c]	5[c]
EAA acceptable (5)	5[a]	5[a]	4[c]		
Continue with exercise and medication (5)	5[b]	5[b]	4.5[a]	5[c]	5[c]
Total number of participants in the study	5	5	2	1	1
Total number of participants in the study with data	4	3	2	1	1

[a]n=2 participants taking either the medication/exercise.

[b]n=3 participants taking either the medication/exercise.

[c]n=1 participant taking either the medication/exercise.

Highest score available for each question within parenthesis.

EPA=eicosapentaenoic acid, PRT=progressive resistance training, EAA=essential amino acids, CU=compassionate use

One Arm A and one Arm B particpant did not complete the acceptability questionaire during compassionate use (CU).

Table 3 Compliance table for individual participants completing compassionate use

	Percentage taken of the total study dose/attendance at sessions				
	EPA	**Celecoxib**	**PRT/Days**	**PRT**	**EAA**
Arm A	100	0	5 sessions	100	21
	25/25 days	0	25 days	5/5	21/100 g
Arm A	4.8	93.9	48 sessions	79.2	0
	8 days*	155 days*	165 days	38/48	0
Arm B	100	100	16 sessions	81.3	93
	53/53 days	53/53 days	53 days	13/16	186/200 g*
Arm B	100	100	21 sessions	85.7	100
	71/71 days	71/71 days	71 days	18/21	420/420 g
Arm B	0	100	25 sessions	32	0
	0	87/87 days	87 days	8/25	0
Arm B	100	100	20 sessions	95	94.7
	67/67 days	67/67 days	67 days	19/20	360/380 g

*participant decision to stop

CU 1 equals 28 doses of EPA and celecoxib, 8 PRT sessions, and 160 g of EAA.

CU 2 equals 56 doses of EPA and celecoxib, 16 PRT sessions, and 320 g of EAA.

CU 3 equals 84 doses of EPA and celecoxib, 24 PRT sessions, and 480 g of EAA.

CU 4 equals 112 doses of EPA and celecoxib, 32 PRT sessions, and 640 g of EAA.

CU 5 equals 140 doses of EPA and celecoxib, 40 PRT sessions, and 800 g of EAA.

EPA=eicosapentaenoic acid, PRT=progressive resistance training, EAA=essential amino acids, CU=compassionate use

Table 4 Percentage compliance table for participants completing compassionate use

	EPA	**Celecoxib**	**PRT**	**EAA**
Arm A	100		100	21
Arm A	4.8	93.9	79.2	
Arm B	100	100	81.3	93
Arm B	100	100	85.7	100
Arm B		100	32	
Arm B	100	100	95	94.7
Mean	**81.0**[a]	**98.8**[b]	**78.9**	**77.2**[c]

[a]n=5 participants taking EPA. One previous Arm B participant declined EPA.

[b]n=5 participants taking celecoxib. One previous Arm A participant did not take celecoxib, due to remaining on diclofenac 100 mg sustained release.

[c]n=4 participants taking EAA. One previous Arm A and one previous Arm B declined EAA.

EPA=eicosapentaenoic acid, PRT=progressive resistance training, EAA=essential amino acids, CU=compassionate use

Secondary endpoints

Individual participant mean weight, FFM, albumin and CRP level, per each study visit, is shown in Table 5. Three participants continued to lose total body weight, and all four participants continued to lose FFM throughout CU visits. At CU 1 (main study week 20 + week 4 CU=24 weeks) there was a mean percentage weight change of −5.6% (range −11.5 to +5.1%, n=3), with a mean FFM change of −3.2% (range −7.0 to +1.8%, n=3). At CU 2 (28 weeks) there was a mean percentage weight change of −6.5% (range −11.0 to +2.2%, n=3), with a mean FFM change of −3.4% (range −4.6 to −1.5%, n=3). At CU 3 (32 weeks) there was a mean percentage weight change of −6.7% (−12.0%, −1.3%, n=2), with a mean FFM change of −4.7% (−8.1%, −1.3%, n=2). For the remaining participant results at CU 4 (36 weeks) there was a percentage weight change of −13.0%, and a FFM change of −7.7%. At CU 5 (40 weeks) there was a

percentage weight change of −12.9%, and a FFM change of −4.6%. This indicates relatively low FFM loss of −3.2% to −4.6% over the 20−week main study, plus a further 4 to 20 weeks during compassionate use.

Table 5 Individual participants secondary outcome results

Arm A		Randomisation	Week 20	CU 1	CU 2	CU 3	CU 4	CU 5
Weight (kg)		70.7	68.2	62.6	62.9	62.2	61.5	61.6
	Difference		−2.5	−8.1	−7.8	−8.5	−9.2	−9.1
	% difference		−3.5%	−11.5%	−11.0%	−12.0%	−13.0%	−12.9%
FFM (kg)		54.6	53.0	50.8	52.3	50.2	50.4	52.1
	Difference		−1.6	−3.8	−2.3	−4.4	−4.2	−2.5
	% difference		−3.0%	−7.0%	−4.2%	−8.1%	−7.7%	−4.6%
Albumin (g/L)		35	35	28	30	34	35	33
	Difference		0	−7	−5	−1	0	−2
	% difference		0.0%	−20.0%	−14.3%	−2.9%	0.0%	−5.7%
CRP (mg/L)		9	12	32	30	13	32	27
	Difference		+3	+23	+21	+4	+23	+18
	% difference		+33.3%	+255.6%	+233.3%	+44.4%	+255.6%	+200.0%
Arm B		**Randomisation**	**Week 20**	**CU 1**	**CU 2**	**CU 3**	**CU 4**	**CU 5**
Weight (kg)		78.9	73.9	70.7	70.4			
	Difference		−5.0	−8.2	−8.5			
	% difference		−6.3%	−10.4%	−10.8%			
FFM (kg)		60.4	58.9	57.7	59.5			
	Difference		−1.5	−2.7	−0.9			
	% difference		−2.5%	−4.5%	−1.5%			
Albumin (g/L)		44	38	41	43			
	Difference		−6	−3	−1			
	% difference		−13.6%	−6.8%	−2.3%			
CRP (mg/L)		37	211	42	62			
	Difference		+174	+5	+25			
	% difference		+470.3%	+13.5%	+67.6%			
Arm B		**Randomisation**	**Week 20**	**CU 1**	**CU 2**	**CU 3**	**CU 4**	**CU 5**
Weight (kg)		78.6	74.6			77.6		
	Difference		−4			−1		
	% difference		−5.1%			−1.3%		
FFM (kg)		47.2	46.1			46.6		
	Difference		−1.1			−0.6		
	% difference		−2.3%			−1.3%		
Albumin (g/L)		40	35			39		
	Difference		−5			−1		
	% difference		−12.5%			−2.5%		
CRP (mg/L)		5	2			4		
	Difference		−3			−1		
	% difference		−60.0%			−20.0%		

Table 5 (Continued)

Arm B		Randomisation	Week 20	CU 1	CU 2	CU 3	CU 4	CU 5
Weight (kg)		45.1	47.1	47.4	46.1			
	Difference		+2	+2.3	+1			
	% difference		+4.4%	+5.1%	+2.2%			
FFM (kg)		39.2	39.8	39.9	37.4			
	Difference		+0.6	+0.7	−1.8			
	% difference		+1.5%	+1.8%	−4.6%			
Albumin (g/L)		25	27	22	23			
	Difference		+2	−3	−2			
	% difference		+8.0%	−12.0%	−8.0%			
CRP (mg/L)		55	46	37	61			
	Difference		−9	−18	+6			
	% difference		−1.4%	−32.7%	+10.9%			

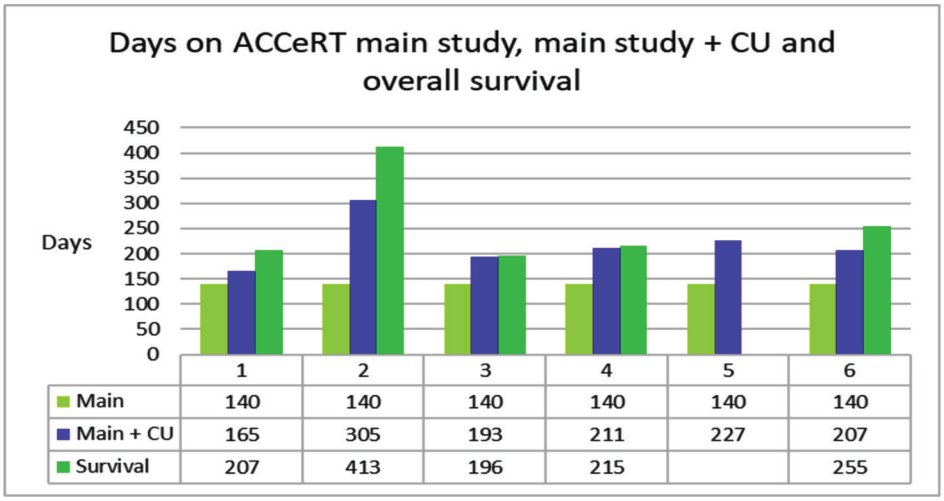
FFM=fat free mass, CRP=C-reactive protein, CU=compassionate use

At CU 1 there was a mean percentage albumin change of −12.9% (range −20.0 to −6.8%, n=3), with a mean CRP change of +78.8% (range −32.7 to +255.6%, n=3). At CU 2 there was a mean percentage albumin change of −8.2% (range −14.3 to −2.3%, n=3), with a mean CRP change of +103.9% (range +10.9 to +233.3%, n=3). At CU 3 there was a mean percentage albumin change of −2.7% (−2.9%, −2.5%, n=2), with a mean CRP change of +12.2% (−20.0%, +44.0%, n=2). For the remaining participant results at CU 4 there was an albumin change of 0% and a CRP change of +255.6%. At CU 5 there was an albumin change of −5.7% and a CRP change of +200.0%. Percentage change was high for one participant, who had a 20.0% reduction in their albumin level during the first cycle of second-line chemotherapy. It is difficult to discuss trends in CRP levels during compassionate use, due to some participants receiving corticosteroids during chemotherapy and radiotherapy; therefore, this not further discussed here.

High scores on the primary endpoint acceptable questionnaire showed that the participants found engaging in the PRT sessions acceptable. At each session, participants were assessed, and the exercise programme was adapted. Results show that both Arm A participants that transferred onto PRT sessions achieved the planned programme and BORG-Rating of perceived exertion (BORG RPE) 11: 'light' at the end of phase I/week 4 (CU 1=total 24 weeks). The designed low volume, low intensity to a moderate volume, and moderate-high intensity training programmes were both safe and acceptable within a NSCLC end-stage cachectic population. Additionally, it was possible to modify the exercise prescription at different time points for each participant, in an individual adaptive manner, due to ongoing chemotherapy, radiotherapy or further disease progression.

As per Figure 2, there was an overall mean time on the main ACCeRT study + CU of 218 days (range 165 to 305) and mean overall survival of 257 days (range 196 to still alive). Interestingly, one participant had relevant stable body weight as well as ECOG-PS and was offered a second line of chemotherapy during CU.

There were no treatment-related deaths, nor exercise-related events, seen within both the main study and during compassionate use. As per the published main study results, there was one possible case of study medication induced atrial fibrillation within one Arm A participant.[14]



	1	2	3	4	5	6
Main	140	140	140	140	140	140
Main + CU	165	305	193	211	227	207
Survival	207	413	196	215		255

*One participant (participant 5) still alive at time of submission.
ACCeRT=Auckland's Cancer Cachexia evaluating Resistance Training, CU=compassionate use

Figure 2 Individual participants days on Auckland's Cancer Cachexia evaluating Resistance Training main study plus compassionate use, and overall survival from main study entry

In summary, the first Arm A participant chose to continue with the daily dose of EPA and to begin PRT and EAA only. This participant was continuing on daily diclofenac 100 mg sustained-release for bilateral hip osteoarthritis pre-study entry and completed compassionate use for 25 days and five PRT sessions. Compassionate treatment and PRT was discontinued by the study team at week 23 (week 20 main study + week 3 CU), due to dislocation of the hip and pelvic pain, and was required to remain in hospital for an extended time. Last recorded ECOG PS=1: there were no other data collected for this participant. The second Arm A participant chose to continue with the daily dose of EPA, celecoxib and to begin PRT only. EAA was declined, due to all the other medications this participant was taking. This participant decided to stop EPA after 8 days of compassionate use, with a compliance of 4.8%. They had completed compassionate use for 165 days and 48 PRT sessions. Compassionate treatment and PRT was discontinued at this participants request at week 44 (week 20 main study + week 24 CU), due to moving to a property outside of the city. Last recorded ECOG PS=2. The first Arm B participant chose to continue with the daily dose of EPA, celecoxib, PRT and EAA, and completed compassionate use for 53 days and 16 PRT sessions: compassionate treatment and PRT was discontinued at week 28 (20 main study + week 8 CU) due to death. Last recorded ECOG PS=2: there were no other data collected for this participant. The second Arm B participant chose to continue with the daily dose of EPA, celecoxib, PRT and EAA, and completed compassionate use for 71 days and 21 PRT sessions. Compassionate treatment and PRT was discontinued at week 31 (week 20 main study + week 11 CU) due to death. Last recorded ECOG PS=2. The third Arm B participant stopped EPA at week 11, and received a reduced dose of EAA from week 3 in the main study, and completed compassionate use for 87 days and 25 PRT (32.0%) sessions. This was due to the logistics of caring for a young family, and attending exercise sessions. Compassionate treatment and PRT was discontinued at the participants request at week 33 (week 20 main study

+ week 13 CU) due to moving to another island. Last recorded ECOG PS=2. The fourth Arm B participant chose to continue with the daily dose of EPA, celecoxib, PRT and EAA, and completed compassionate use for 67 days and 20 PRT sessions. Compassionate treatment and PRT was discontinued by the study team at week 10 (week 20 main study + week 10 CU), due to progression of disease and the requirement for hospice respite care. Last recorded ECOG PS=2.

Discussion

The continuation of the ACCeRT study regimen under compassionate use further demonstrates the feasibility and acceptability in patients with refractory cancer cachexia and NSCLC. The multi-targeted regimen has shown further safety without any exercise-induced adverse events.

It was observed that three of the four participants in the 24th week of the intervention still experienced an overall loss of total body weight and FFM. The additional data gained post week 20/EOT visit helps support the longer study time period utilised within the main ACCeRT study, along with gaining new data in this population over an extended time period.

Median survival within the ACCeRT main study of 96 days within Arm A (EPA + celecoxib), versus 136 days within Arm B (EPA, celecoxib, PRT + EAA), versus 257 days in the main ACCeRT study + CU (one participant still alive at submission), is comparable to the followings of two randomized controlled trials (RCT) in late cachexia/refractory cachexia; wherein anti-cancer treatment was not permitted. Gordon et al., investigated the use of 200 mg thalidomide OD verses a placebo in advanced pancreatic cancer patients, with at least a 10.0% weight loss over the previous six months; with a planned study period of 24 weeks. Fifty patients were randomised (1:1), with 20 participants achieving eight weeks of treatment. There was a median survival of 148 days within the thalidomide group versus 110 days within the placebo group (p-value=0.450).[15]

This was followed by the RCT of EPA versus placebo within lung and gastrointestinal cancer patients, with ≥5.0% of weight loss of pre-illness stable weight. Participants were randomised to either 4 g EPA, 2 g EPA, or a placebo OD. There was a study period of eight weeks, with participants permitted to continue with EPA post EOT under compassionate use.[16] Five hundred and eighteen patients were randomised (1:1:1), with 50.0% achieving eight weeks of treatment. There was a median overall survival of 142 days within 4 g EPA, versus 155 days within 2 g EPA, versus 140 days within the placebo group (p-value=0.750). This is in contrast to the survival data within the ROMANA 1 and 2 studies.[17,18] Whereas, these results showed no difference between groups with median survival over one year of 8.9 months (~270 days) within the anamorelin group versus 9.2 months (~280 days) within the placebo group (p-value=0.470). Additionally, similar survival rates were seen between groups, with deaths of 10.5% in the anamorelin group versus 13.8% within the placebo group in the ROMANA 3 extension study.[18]

Other studies, within the pre-cachexia/cachexia phase, have included the Espindolol study, which again showed no significant difference in survival between the high-dose group (61 weeks, ~427 days), low-dose group (50.9 weeks, ~356 days) and placebo group (42.3 weeks, ~296 days).[19] The only other multi-targeted study (Pre-MENAC) showed a median survival of 10 months (~304 days) within the treatment group versus 8 months (~243 days) within the control group (p-value=0.570).[11] A non-significant difference in overall survival was seen between groups in the phase II Enobosarm study, again in patients with pre-cachexia/cachexia.[20] Interestingly, none of the above studies have shown an overall survival benefit by addressing pre-cachexia/cachexia in patients undergoing anti-cancer treatment.

ACCeRT is the first study to investigate a multi-targeted regimen; including the use of exercise, in a refractory cachexia population. High mean acceptability scores of 4 and 5 were maintained throughout CU.

The ACCeRT study was appropriately designed to evaluate the feasibility of a conservative PRT protocol (given cachexia patient considerations). As PRT was well tolerated during the CU phase, future studies should look to optimise the PRT to minimise muscle wasting, and maintain patient functional outcomes e.g., activities of daily living, and fatigue.

The ACCeRT CU data has a number of limitations. Firstly, the attrition rate within both Arms within the main study, with two allocated to Arm A and four allocated to Arm B proceeding onto this compassionate use study. Interestingly, participants who continued post week 12 study visit, then went on and completed the week 20/EOT study visit and then further continued with post study CU. Secondly, it must be acknowledged that the open-label design, and that participants could decide on which elements of the regimen to continue with increases the risk of bias of these results. Thirdly, CU body composition was limited to BIA data only, additional CU MRI analysis would have strengthened the skeletal muscle changes.

Conclusion

In conclusion ACCeRT is the first study to utilise a multi-targeted regimen in the refractory cancer population; therefore, a comparison with other research studies cannot be made at this point. The post main ACCeRT study CU results indicate that patients may benefit from being enrolled onto a multi-targeted cachexia symptom management treatment regimen, even during the late/refractory stage.

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Conflict of interest

All authors declare that they have no competing interests.

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