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

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Summary

Background Patients with advanced cancer frequently experience anorexia and cachexia, which are associated with reduced food intake, altered body composition, and decreased functionality. We assessed anamorelin, a novel ghrelin-receptor agonist, on cachexia in patients with advanced non-small-cell lung cancer and cachexia.

Methods ROMANA 1 and ROMANA 2 were randomised, double-blind, placebo-controlled phase 3 trials done at 93 sites in 19 countries. Patients with inoperable stage III or IV non-small-cell lung cancer and cachexia (defined as ≥5% weight loss within 6 months or body-mass index <20 kg/m²) were randomly assigned 2:1 to anamorelin 100 mg orally once daily or placebo, with a computer-generated randomisation algorithm stratified by geographical region, cancer treatment status, and weight loss over the previous 6 months. Co-primary efficacy endpoints were the median change in lean body mass and handgrip strength over 12 weeks and were measured in all study participants (intention-to-treat population). Both trials are now completed and are registered with ClinicalTrials.gov, numbers NCT01387269 and NCT01387282.

Findings From July 8, 2011, to Jan 28, 2014, 484 patients were enrolled in ROMANA 1 (323 to anamorelin, 161 to placebo), and from July 14, 2011, to Oct 31, 2013, 495 patients were enrolled in ROMANA 2 (330 to anamorelin, 165 to placebo). Over 12 weeks, lean body mass increased in patients assigned to anamorelin compared with those assigned to placebo in ROMANA 1 (median increase 0·99 kg [95% CI 0·61 to 1·36] *vs* –0·47 kg [–1·00 to 0·21], p<0·0001) and ROMANA 2 (0·65 kg [0·38 to 0·91] *vs* –0·98 kg [–1·49 to –0·41], p<0·0001). We noted no difference in handgrip strength in ROMANA 1 (–1·10 kg [–1·69 to –0·40] *vs* –1·58 kg [–2·99 to –1·14], p=0·15) or ROMANA 2 (–1·49 kg [–2·06 to –0·58] *vs* –0·95 kg [–1·56 to 0·04], p=0·65). There were no differences in grade 3–4 treatment-related adverse events between study groups; the most common grade 3–4 adverse event was hyperglycaemia, occurring in one (<1%) of 320 patients given anamorelin in ROMANA 1 and in four (1%) of 330 patients given anamorelin in ROMANA 2.

Interpretation Anamorelin significantly increased lean body mass, but not handgrip, strength in patients with advanced non-small-cell lung cancer. Considering the unmet medical need for safe and effective treatments for cachexia, anamorelin might be a treatment option for patients with cancer anorexia and cachexia.

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Introduction

Anorexia and cachexia are devastating results of cancer and commonly coexist in patients with advanced disease.[1] Although both are multifactorial in origin, anorexia often manifests as decreased appetite and food intake, whereas cachexia is characterised by loss of bodyweight and lean body mass.[2] Weight loss in patients with cancer cachexia is due to a variable combination of decreased oral intake and metabolic change, leading to negative protein and energy balance.[3] Patients with cancer cachexia frequently experience decreased quality of life, reduced chemotherapy tolerance, reduced physical functioning, and shortened survival.[3–6] Between 50% and 80% of patients with advanced cancer develop cachexia, with highest incidence reported in patients with lung and gastrointestinal cancer.[7]

Despite the high prevalence of cancer cachexia, few therapeutic options exist and there is no standard of care for its management. The cause of the condition is multifactorial, and a single-modality approach is unlikely to reverse all aspects of the syndrome and result in durable clinical benefits. Indeed, cachexia is thought to require a comprehensive intervention, including nutrition, exercise, and drugs. However, development of an evidence base for individual treatments is necessary to ultimately build an effective multimodality intervention.[1] To address both nutrition and symptom burden, an ideal drug would improve anorexia and enhance food intake while also stimulating anabolism, thus overcoming the catabolic drive associated with cachexia and increasing lean body mass and bodyweight. Although several available drugs can improve patients' appetite or increase their bodyweight, none can substantially affect lean body mass and its key functional element, skeletal muscle.[8,31] Additionally, corticosteroids and progestational drugs,

Research in context

Evidence before this study

Although cachexia has long been recognised as a substantial source of morbidity and mortality in patients with cancer, treatment options are scarce. We did a literature review with PubMed from Jan 3, 2005, to Jan 3, 2015, with the terms "cancer" and "cachexia" and/or "anorexia" and "weight loss", confirming the absence of evidence supporting the use of approved medications for the treatment of cancer cachexia. A systematic review of the treatment of cancer-associated anorexia concluded that progestins and corticosteroids are effective in increasing patients' appetite and weight, but had no effect on cachexia. Two Cochrane Database reviews of megestrol acetate, the most commonly used progestin for cancer-associated anorexia and cachexia, similarly concluded that use of megestrol acetate is associated with improvement in appetite and only slight weight gain. However, the more recent review noted that oedema, thromboembolic events, and death were frequent complications of megestrol acetate, and recommended that patients are informed of the risks associated with the drug. A comprehensive literature review of treatment options in cancer cachexia concluded that there are no available drugs for the treatment of cancer cachexia.

Added value of this study

We show in two international phase 3 clinical trials that patients with advanced non-small-cell lung cancer and cachexia who received anamorelin consistently increased lean body mass as well as bodyweight over the 12-week study period. Importantly, patients also had an improvement in their anorexia–cachexia symptoms.

Implications of all the available evidence

Anamorelin is an effective and well tolerated drug for the treatment of patients with advanced non-small-cell lung cancer and cachexia, and might be a novel treatment for such patients.

which are the most commonly used drugs in patients with anorexia, have substantial adverse events and potential toxic effects, which can include catabolism and muscle wasting.[9,10]

Anamorelin is an orally active, high-affinity, selective ghrelin-receptor agonist.[11] Ghrelin is the natural ligand for the G-protein-coupled ghrelin receptor, which when activated has anabolic and appetite-stimulating effects.[12] These effects are partly mediated through transient increases in growth hormone and insulin-like growth factor (IGF-1). Several double-blind, randomised phase 2 studies[13–15] in patients with advanced cancer have shown that anamorelin is safe and efficacious in increasing patients' lean body mass, bodyweight, and appetite.

See Online for appendix

In theory, an effective treatment for cancer-associated muscle wasting, a key component of the cachexia, should improve muscle mass and, as a consequence, increase muscle strength. However, muscle wasting in patients with cancer is complex, arising from diverse factors such as age-related sarcopenia, cancer therapy, and comorbidity, in addition to the tumour. Moreover, muscle strength might not only be related to muscle mass, but also to other factors, such as persisting systemic inflammation and associated fatigue. A previous phase 2 study[13] with anamorelin showed a significant effect on handgrip strength over a 12-week treatment period, whereas a subsequent phase 2 study did not.[15] In the absence of an alternative internationally agreed standard for muscle strength and function, we assessed the efficacy with lean body mass and handgrip strength as co-primary endpoints and safety of anamorelin compared with placebo in two international, double-blind, phase 3 studies in patients with advanced non-small-cell lung cancer and cachexia.

Methods

Study design and participants

ROMANA 1 and ROMANA 2 were two international, double-blind, placebo-controlled, randomised phase 3 studies. Two identical trials were done as per regulatory advice in order to have evidence from two adequate and well-controlled trials. ROMANA 1 was done at 54 hospital and community sites in 15 countries between July 8, 2011, and Jan 28, 2014, and ROMANA 2 was done at 39 hospital and community sites in seven countries between July 14, 2011, and Oct 31, 2013 (see appendix p 1–2 for list of participating investigators).

Eligible patients were at least 18 years of age; had histologically confirmed unresectable stage III or IV non-small-cell lung cancer; had cachexia (defined as involuntary weight loss of ≥5% within the previous 6 months, or body-mass index [BMI] <20 kg/m²); and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 (on a scale of 0–5, with 0 indicating that the patient is asymptomatic and higher numbers indicating increasing disability). Eligible patients could begin a new line of chemotherapy or radiotherapy within 14 days of randomisation, be receiving maintenance chemotherapy, or have completed chemotherapy or radiotherapy more than 14 days before randomisation with no plan to initiate additional treatment during the study period. Patients were required to have a life expectancy of at least 4 months, adequate hepatic function (defined as aspartate amino transferase and alanine amino transferase concentrations ≤5 x the upper limit of normal [ULN]), and adequate renal function (defined as creatinine concentrations ≤2 x ULN, or calculated creatinine clearance >30 mL per min). Patients with known brain metastases or uncontrolled diabetes were not eligible for study participation. Patients taking prescription medications

intended to increase appetite or treat weight loss were also excluded. All patients provided written informed consent. The study protocols were approved by the institutional review board or independent ethics committee at each participating centre and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice Guidelines, and the Declaration of Helsinki.

Randomisation and masking

Patients were randomly assigned (2:1) to anamorelin hydrochloride or placebo by a centrally managed, dynamic, computer-generated randomisation algorithm (Medpace, Cincinnati, OH, USA). Randomisation was stratified by geographical region (North America *vs* rest of world), by cancer treatment status (initiating new chemotherapy or radiation, or receiving maintenance chemotherapy *vs* no treatment), and by weight loss during the previous 6 months (≤10% of bodyweight *vs* >10% of bodyweight). A dynamic randomisation based on a minimisation algorithm for each study was used rather than a randomisation schedule because it enhanced the likelihood of achieving balance within each stratum and in the overall treatment group. The randomisation algorithm also used study site as a factor to ensure relative balance for data integrity and efficient drug supply use. Prepackaged anamorelin or identical placebo tablets were provided to maintain the double-blind study design. The randomisation algorithm assigned drug numbers at random, on the basis of the treatment assignment and drug numbers available at the site. Research staff used these drug numbers to provide eligible patients with the correct drug supply kits. Research staff assessing outcomes and analysing data were masked to the patients' assigned intervention group throughout the study.

Procedures

Patients received either oral 100 mg anamorelin hydrochloride or placebo (Pharmaceutics International, Hunt Valley, MD, USA) once daily for the 12-week study period. At the end of this period, patients had the

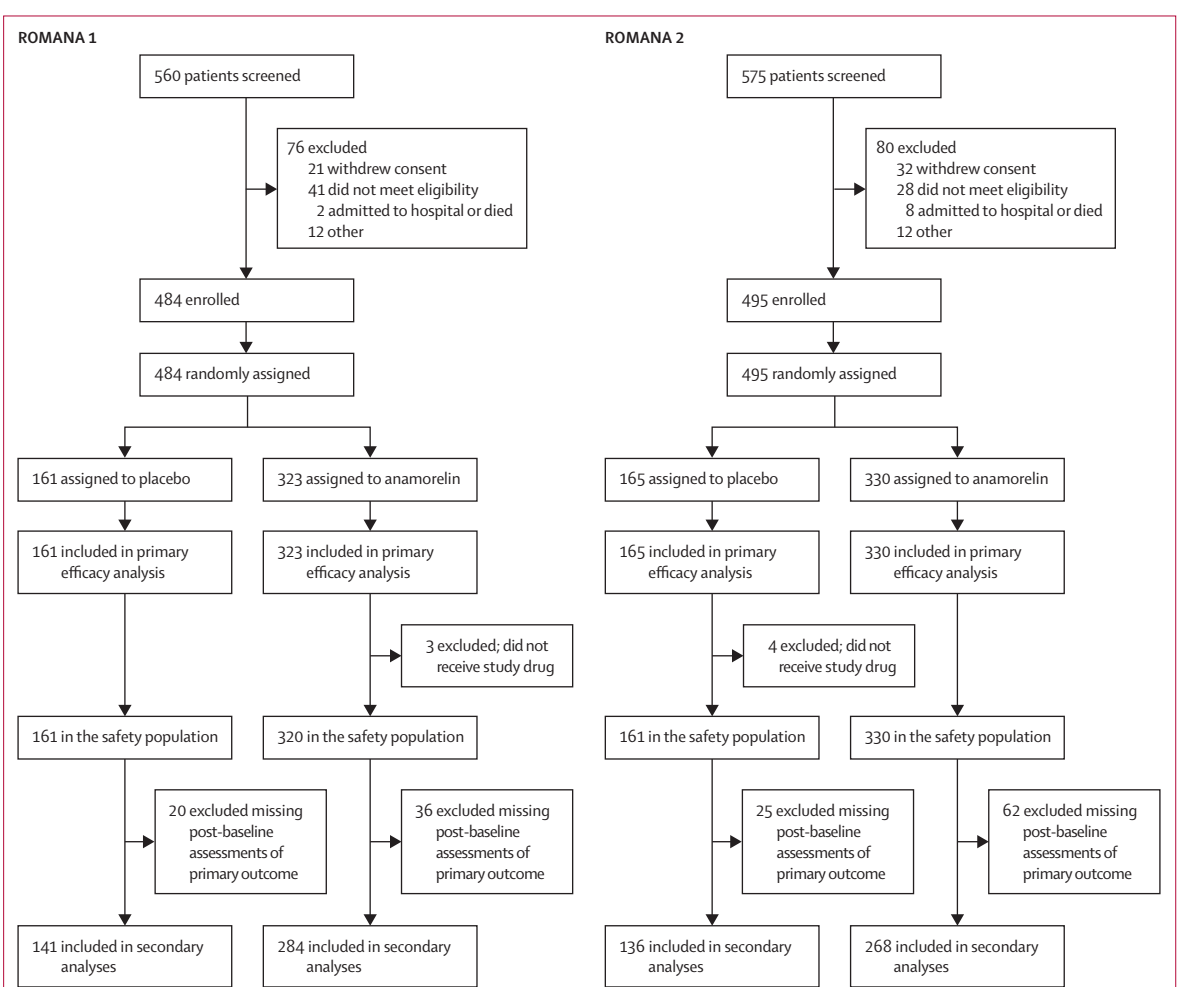

Figure 1: **Trial profiles for ROMANA 1 and ROMANA 2 trials**

	ROMANA 1		ROMANA 2	
	Anamorelin (n=323)	Placebo (n=161)	Anamorelin (n=330)	Placebo (n=165)
Age (years, range)	63 (30–86)	63 (39–83)	63 (36–86)	62 (33–88)
Sex				
Men	247 (76%)	121 (75%)	240 (73%)	122 (74%)
Women	76 (24%)	40 (25%)	90 (27%)	43 (26%)
Ethnic origin				
White	319 (99%)	159 (99%)	326 (99%)	162 (98%)
Black	1 (<1%)	0	2 (<1%)	1 (1%)
Asian	1 (<1%)	0	0	1 (1%)
Other/unknown	2 (<1%)	2 (1%)	2 (<1%)	1 (1%)
ECOG performance status				
0	40 (12%)	16 (10%)	26 (8%)	10 (6%)
1	218 (67%)	119 (74%)	215 (65%)	114 (69%)
2	64 (20%)	26 (16%)	89 (27%)	41 (25%)
Missing/unknown	1 (<1%)	0	0	0
CRP				
>10 mg/L	210 (65%)	113 (70%)	212 (64%)	107 (65%)
Disease stage at study entry				
IIIA	19 (6%)	16 (10%)	29 (9%)	16 (10%)
IIIB	48 (15%)	30 (19%)	62 (19%)	36 (22%)
IV	256 (79%)	114 (71%)	238 (72%)	113 (68%)
Missing	0	1 (<1%)	1 (<1%)	0
Histology				
Adenocarcinoma	141 (44%)	70 (43%)	119 (36%)	69 (42%)
Squamous cell	145 (45%)	80 (50%)	163 (49%)	71 (43%)
Large cell	13 (4%)	3 (2%)	13 (4%)	6 (4%)
Other	27 (8%)	12 (7%)	35 (11%)	19 (12%)
Geographical region				
North America	35 (11%)	17 (11%)	10 (3%)	5 (3%)
West Europe	122 (38%)	62 (39%)	142 (43%)	75 (45%)
East Europe and Russia	166 (51%)	82 (51%)	164 (50%)	77 (47%)
Australia	0	0	14 (4%)	8 (5%)
Present cancer treatment*				
Chemotherapy for active disease	275 (85%)	134 (83%)	225 (68%)	101 (61%)
Maintenance chemotherapy	11 (3%)	7 (4%)	32 (10%)	25 (15%)
Adjuvant chemotherapy	3 (1%)	0	6 (2%)	1 (<1%)
Any radiotherapy	38 (12%)	18 (11%)	31 (9%)	14 (8%)
Median time from initial tumour diagnosis to study entry (months, range)	8·5 (0·4–184)	6·3 (0·3–153)	9·8 (0·5–239)	8·3 (0·3–95)
Median handgrip strength (kg)	31·90 (24·6–40·0)	31·80 (22·0–41·2)	28·00 (19·8–36·7)	28·40 (20·5–36·9)
Median LBM (kg)	46·3 (40·1–51·9)	46·6 (39·1–52·2)	43·8 (38·7–49·1)	43·6 (38·4–48·9)

(Table 1 continues on next page)

option to enrol in an extension study (ROMANA 3), continuing to receive their assigned treatment for an additional 12 weeks. The ROMANA 3 results will be published separately. Patients could withdraw at any time or at the discretion of the investigator because of adverse events requiring study drug cessation or major protocol violation. No dose reductions or interruptions were planned.

Body composition (lean body mass, total body mass, fat mass, and appendicular lean body mass [lean body mass of the arms and legs only]) was measured with dual-energy X-ray absorptiometry (DXA) with Hologic (Bedford, MA, USA) or GE Lunar (Wauwatosa, WI, USA) absorptiometers. Scans were assessed at a central reading facility (Medpace Imaging, Cincinnati, OH, USA). Handgrip strength was measured in the non-dominant hand with hand-held dynamometers (Tracker Freedom Wireless Grip Strength Testing System; JTECH Medical, Midvale, UT, USA). These endpoints were measured at baseline (within 2 weeks before randomisation), and at 6 and 12 weeks. Bodyweight was measured with a calibrated scale dedicated for use in these studies. Patients were weighed wearing only a hospital gown or scrubs and without shoes. Symptom burden was measured with the anorexia–cachexia and fatigue scales from the Functional Assessment of Cancer Therapy (FACT) Measurement System (The FAACT tool mentioned in the protocol is composed of the FACT scale and the anorexia–cachexia scale, and the FACIT-F tool is composed of the FACT scale and the fatigue scale).[16,17] The 12-item anorexia–cachexia scale is scored ranging from 0 to 48, and the 13-item fatigue scale is scored ranging from 0 to 52, with higher scores showing lower symptom burden. Bodyweight and symptom burden were collected at baseline and every 3 weeks throughout the study period. Study participants were followed up for survival for 1 year.

Treatment-emergent adverse events with an onset date on or after the date of the first drug dose and including 7 days after the last drug dose were graded by the site investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Outcomes

The co-primary endpoints were the change in lean body mass and handgrip strength over the 12-week study period. For these endpoints, the change from baseline over 12 weeks was defined as the average of the change from baseline at week 6 and change from baseline at week 12. This strategy was chosen because averaging the change from baseline across the two post-dose timepoints was deemed to be a more conservative approach compared with using only the week 12 data.

Secondary endpoints were the change from baseline over 12 weeks in bodyweight (measured by scale), and symptoms of anorexia–cachexia and fatigue. Pooled overall survival at 1 year was an additional secondary endpoint. Other protocol-defined secondary endpoints, that are not reported here, were additional analyses of lean body mass, handgrip strength, and scores from the

FACT instruments (the anorexia–cachexia and the fatigue domains from the FACT measuring system). Exploratory endpoints included change in other body composition variables (total body mass, fat mass, and appendicular lean body mass) from baseline to week 12.

Statistical analysis

In a phase 2 clinical trial,[15] the standard deviation (SD) for handgrip strength (4·9 kg) was noted to be greater than the SD for lean body mass; therefore, the sample size calculation was based on handgrip strength. ROMANA 1 and 2 were designed with 90% power to detect a change of 2·0 kg from baseline over 12 weeks between study groups in both lean body mass and handgrip strength with a two-sample *t* test with a two-sided significance level of 0·05. The calculated sample size of 288 was adjusted to 333 by dividing by a factor of 0·864 to account for the planned non-parametric analysis of the primary endpoints. The final sample size for both studies was 477, to account for an expected 30% dropout rate.

All randomly assigned patient populations followed the intention-to-treat (ITT) principle. For the co-primary endpoints, the change from baseline over 12 weeks included two measurements (at week 6 and week 12), and for secondary endpoints the change from baseline over 12 weeks included several repeated measurements (baseline, week 3, week 6, week 9, and week 12). Therefore, different methods were used for the analyses of the primary and secondary endpoints, and different approaches were used to account for selective attrition in primary and secondary endpoints.

Co-primary efficacy endpoints of lean body mass and handgrip strength were assessed in all randomly assigned patients. The following covariates were used in the treatment comparison and in the multiple imputation model: ECOG performance status (0–1 *vs* 2), BMI (>18·5 kg/m² *vs* ≤18·5 kg/m²), age (>65 years *vs* ≤65 years), gender, weight loss over the previous 6 months (>10% *vs* ≤10%), geographical region (USA *vs* non-USA), chemotherapy or radiotherapy status, and baseline lean body mass and baseline handgrip strength. To assess the treatment difference for the co-primary efficacy endpoints, we used modified Wilcoxon rank sum test whereby death was regarded as an outcome of the study and not missing data. These primary composite endpoints did not have an assumption of normal distribution. The primary analysis for the co-primary endpoints were based on ranks. Ranking order was established both by the change from baseline in lean body mass or the change in handgrip strength over 12 weeks and by survival time, with lower ranks representing worse outcomes for each endpoint. Under the null hypothesis of no treatment effect, there was to be no difference in the ranks between the two treatment groups based on each of the co-primary endpoints. To account for selective attrition, missing post-baseline values were handled by multiple imputation and ranking methods with assumptions that patients with similar covariates and lean body mass or handgrip strength values (as available) would have similar distribution of lean body mass or handgrip strength values at the post-baseline visits. The 95% CIs for the median change from baseline over 12 weeks, calculated by bootstrap simulations associated with Wilcoxon rank sum test procedure, are provided for each treatment group along with p values for treatment difference. Global sensitivity analyses for the co-primary endpoints were done to assess the sensitivity of inferences to the benchmark assumptions. Because the primary endpoints are composite endpoints of lean body mass or handgrip strength and survival, a post-hoc analysis based on last value carried forward and analysis in those patients who survived 12 weeks were also done for both primary and secondary endpoints with a parametric model that adjusts for stratifying covariates. Prespecified subgroup analyses for the change in lean body mass and handgrip strength from baseline over 12 weeks by treatment group were done with the same method for the primary endpoints.

Secondary endpoints of bodyweight and symptom burden were assessed in patients who received any study drug and for whom at least one post-baseline primary efficacy result was obtained (modified intention-to-treat

	ROMANA 1		ROMANA 2	
	Anamorelin (n=323)	Placebo (n=161)	Anamorelin (n=330)	Placebo (n=165)
(Continued from previous page)				
Additional body composition parameters† (kg)				
Median total body mass	68·0 (58·7–77·3)	68·1 (58·8–77·0)	64·5 (55·2–73·8)	60·8 (54·6–72·1)
Median fat mass	18·9 (12·9–24·7)	20·2 (14·1–25·8)	17·7 (11·8–23·3)	16·6 (10·6–22·2)
Median appendicular LBM (LBM of arms and legs)	20·0 (16·5–22·4)	19·7 (16·0–23·5)	19·0 (15·8–21·5)	18·2 (15·7–21·8)
Mean body weight (kg)	67·6 (13·0)	68·0 (13·3)	63·9 (13·3)	62·7 (12·9)
Self-reported weight loss in previous 6 months				
≤10% of body weight	195 (60%)	98 (61%)	171 (52%)	86 (52%)
>10% of body weight	128 (40%)	63 (39%)	159 (48%)	79 (48%)
Mean BMI (kg/m²)	23·2 (3·6)	23·3 (3·7)	22·5 (3·7)	22·1 (3·7)
Symptom measures				
Mean anorexia–cachexia scale‡	29·9 (8·4)	29·9 (8·7)	27·6 (8·8)	28·8 (8·6)
Mean fatigue scale§	30·6 (11·1)	30·9 (10·7)	27·6 (10·7)	28·6 (10·8)

Data are in n (%), mean (SD), or median (IQR) unless reported otherwise. Percentage is calculated with the number of patients in the column heading as the denominator. ECOG=Eastern Cooperative Oncology Group. CRP=C-reactive protein. LBM=lean body mass. BMI=body-mass index. *Patients might have been receiving concurrent chemotherapy and radiotherapy. †Additional body composition parameters were measured via dual energy X-ray absorptiometry as specified per protocols at the same time LBM was assessed; data for these additional body composition parameters were summarised by treatment group as a post-hoc exploratory analysis. ‡12-item anorexia–cachexia scale of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT), with scores ranging from 0 to 48 and higher scores suggesting lower levels of anorexia–cachexia. §13-item fatigue scale of the Functional Assessment of Chronic Illness Therapy-Fatigue, with scores ranging from 0 to 52 and higher scores suggesting less fatigue.

Table 1: **Baseline characteristics**

population). Because we used several measurements (at baseline, week 3, week 6, week 9, and week 12) to collect data for these secondary endpoints, we used longitudinal analysis to assess the treatment effect over time. Treatment differences and p values were estimated with pattern mixture repeated measures models taking into account change from baseline to each post-baseline timepoint. Briefly, this analysis considered the same covariates as for the primary endpoints (ECOG, BMI, age, gender, weight loss over the previous 6 months, geographical region, chemotherapy or radiotherapy status, and baseline bodyweight or symptom burden measures); patients were also stratified into groups based on time or reason for study dropout for analysis. Values were reported as least-squares means with standard error. Missing values for these secondary endpoints were not imputed. The pattern mixture repeated measurement model allowed us to handle missing data and minimise bias. This model treats death as missing data and uses available data from the missing and alive patients separately.

Overall survival over 1 year was assessed with the Kaplan-Meier method and stratified log-rank test for both studies pooled. The Cox proportional hazard model used treatment and stratification factors at randomisation as explanatory variables. Because both trials had identical study design and eligibility criteria, overall survival data were planned a priori to be combined for these two studies to provide a more comprehensible assessment. Additional survival analysis was also done for each individual trial. Per-protocol patients were followed up for survival for 1 year after randomisation. The total follow-up time included the protocol-specified 12 months plus a 3-week window to account for actual visit scheduling. Safety was assessed in all randomly assigned patients who received any study drug.

All statistical tests were two-sided and p values of 0·05 or less were deemed statistically significant. SAS (version 9·2 or above) was used for data analysis. An independent data monitoring committee (DMC), consisting of two clinicians who were not study investigators and one biostatistician, was responsible for doing periodic safety reviews for these studies. A detailed DMC charter was developed before the safety review and, at all DMC meetings done during these studies, the committee confirmed an acceptable risk–benefit profile and recommended the trials continue as planned without the need for modifications to the protocol.

These studies were registered with ClinicalTrials.gov, numbers NCT01387269 (ROMANA 1) and NCT01387282 (ROMANA 2).

Role of the funding source

The study sponsor, Helsinn Therapeutics (US), was involved in study design, provision of study materials, data collection and interpretation, and writing of the report. All authors had full access to the raw data, and JF, YY, EMD, and KCF were involved in data analysis. The corresponding author (JST) was the primary author of the report and had the final decision to submit for publication.

Results

From July 8, 2011, to Jan 28, 2014, 484 patients were enrolled in ROMANA 1, and from July 14, 2011, to Oct 31, 2013, 495 patients were enrolled in ROMANA 2 (figure 1). In ROMANA 1, 161 patients were randomly assigned to placebo and 323 to anamorelin. Of the 481 treated patients in ROMANA 1, 354 (74%) completed treatment and 89 (19%) died during the 12-week study period (patients who died during the 12-week treatment period but had secondary endpoint assessments at week 3, 6, or 9 were included in the analysis because they have post-dose assessments). In ROMANA 2, 165 patients were assigned to placebo and 330 to anamorelin. Of the 491 treated patients in ROMANA 2, 354 (72%) completed treatment and 69 (14%) died during the 12-week study period. The cutoff date for data collection, other than survival, was March, 2014, for ROMANA 1 and December, 2013, for ROMANA 2. Survival follow-up was completed in October, 2014.

Table 1 shows demographic and baseline characteristics in treatment groups in each study. Most patients received chemotherapy during the treatment period.

	ROMANA 1			ROMANA 2		
	Anamorelin	Placebo	p value	Anamorelin	Placebo	p value
Primary endpoints* (n)	323	161		330	165	
Median lean body mass (kg)	0·99 (0·61 to 1·36)	−0·47 (−1·00 to 0·21)	<0·0001	0·65 (0·38 to 0·91)	−0·98 (−1·49 to −0·41)	<0·0001
Median handgrip strength (kg)	−1·10 (−1·69 to −0·40)	−1·58 (−2·99 to −1·14)	0·15	−1·49 (−2·06 to −0·58)	−0·95 (−1·56 to 0·04)	0·65
Secondary endpoints† (n)	284	141		268	136	
Mean bodyweight (kg)	2·20 (0·33)	0·14 (0·36)	<0·0001	0·95 (0·39)	−0·57 (0·44)	<0·0001
Mean anorexia–cachexia scale score	4·12 (0·75)	1·92 (0·81)	0·0004	3·48 (0·94)	1·34 (1·03)	0·0016
Fatigue scale	0·26 (0·89)	−1·91 (0·93)	0·054	1·37 (1·17)	1·23 (1·29)	0·86

Data for primary endpoints are median (95% CI) or for secondary endpoints are mean (SE). *For primary efficacy analysis, change from baseline over 12 weeks per patient was defined as the average of the change from baseline at week 6 and the change from baseline at week 12. p values were obtained from Wilcoxon rank sum test, taking into account missing post-baseline values (ie, imputation), whereby lower ranks represent worse outcomes. †For secondary efficacy analysis, least-squares means, SEs, CIs, and p values were from a mixed-effects pattern mixture repeated measures model.

Table 2: **Changes in primary and secondary efficacy measures from baseline over 12 weeks**

Concurrent chemotherapy regimens are listed in the appendix (p3); most patients received platinum compounds during the 12-week study period. A post-hoc analysis of baseline characteristics showed that patients in ROMANA 2 were further into their disease trajectory than those in ROMANA 1 (appendix p 4), with a median time from diagnosis of 9·7 months (range 0·3–239) in ROMANA 2 versus 7·9 months (0·3–184) in ROMANA 1 (p=0·023). Additionally, a higher proportion of patients had an ECOG performance status of 2 in ROMANA 2 than in ROMANA 1 (table 1; p=0·0041). More patients were receiving no cancer treatment in ROMANA 2

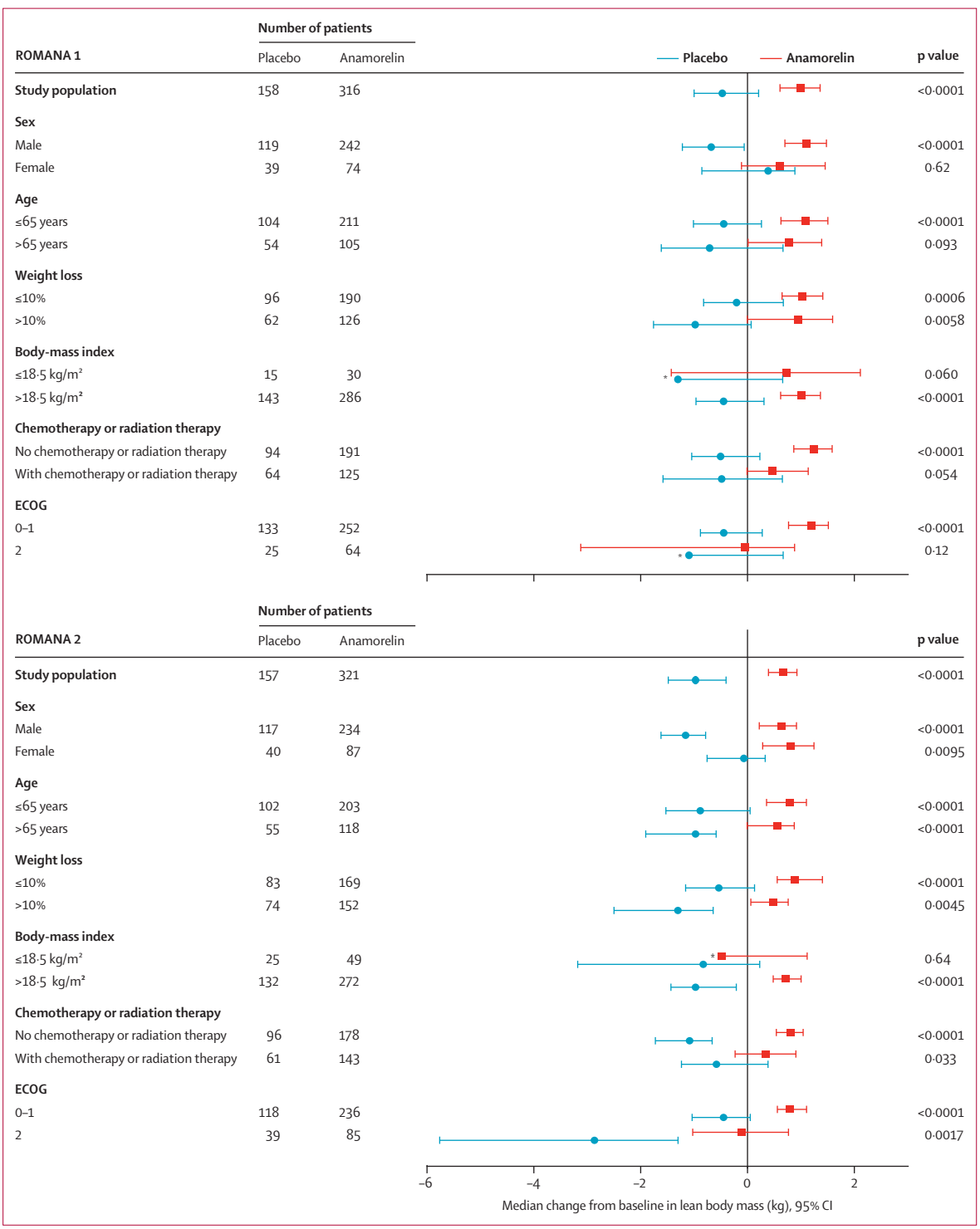

***Figure 2*: Analysis of change in lean body mass (kg) from baseline over 12 weeks by subgroup**
The results are shown as median change from baseline over 12 weeks and 95% CI. The median change from baseline over 12 weeks was defined as the average of the change from baseline at week 6 and the change from baseline at week 12. The red line represents anamorelin 100 mg and the blue line represents placebo. ECOG=Eastern Cooperative Oncology Group. *Shows where lower-bound 95% CI was based on survival days as part of the multiple imputation method of analysis, as described in Methods.

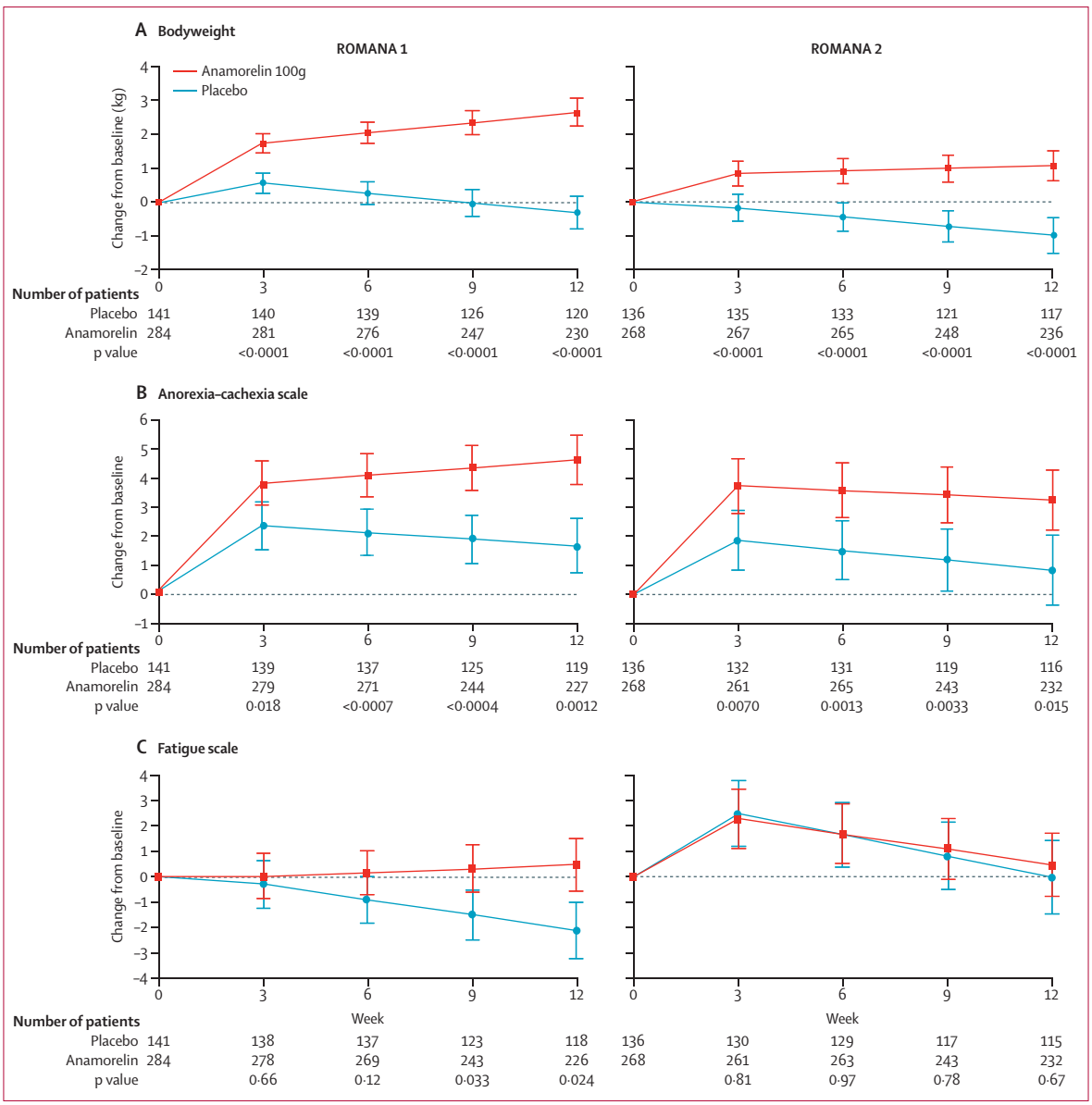

Figure 3: **Change over time in secondary efficacy measures**
(A) The least-squares mean (SE) change from baseline to each timepoint in bodyweight. (B) The least-squares mean (SE) change from baseline to each timepoint in the 12-item anorexia–cachexia scale of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT), with scores ranging from 0 to 48 and increasing scores showing improvement. (C) The least-squares mean (SE) change from baseline to each timepoint in the 13-item fatigue scale of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), with scores ranging from 0 to 52 and increasing scores indicating improvement.

(114 [23%] of 495 patients) than those who did not in ROMANA 1 (57 [12%] of 484; p<0·0001), and patients in ROMANA 2 also had lower lean body mass, bodyweight, and BMI, and higher symptom burden than the ROMANA 1 population (table 1). The number of patients with more than 10% bodyweight loss in the previous 6 months was 238 (48%) of 495 patients in ROMANA 2 and 191 (39%) of 484 patients in ROMANA 1 (p=0·0069).

The median increase in lean body mass over 12 weeks in the anamorelin group was significantly larger than that of the placebo group in both ROMANA 1 and ROMANA 2 (table 2). No differences in handgrip strength were noted between study groups in either trial (table 2). These results are consistent with those obtained from post-hoc analyses of changes in lean body mass and handgrip strength in patients who survived to 12 weeks, or those based on last value carried forward (appendix p 5); these alternate analysis methods were done to show that excluding patients who died or handling missing data differently still provides similar results. Subgroup analysis showed that anamorelin had a significant effect on lean body mass compared with placebo for most subgroups in both ROMANA 1 and

	ROMANA 1			ROMANA 2		
	Anamorelin (n=284)	Placebo (n=141)	p value	Anamorelin (n=268)	Placebo (n=136)	p value
Total body mass	2·87 (0·6 to 5·1)	0·07 (–2·9 to 2·7)	<0·0001	2·04 (–0·5 to 4·7)	–0·59 (–2·1 to 1·6)	<0·0001
Fat mass	1·21 (–0·2 to 2·8)	–0·12 (–0·1 to 1·0)	<0·0001	0·77 (–0·8 to 2·4)	0·09 (–1·1 to 1·1)	0·012
LBM	1·79 (0·2 to 3·4)	0·08 (–1·5 to 1·9)	<0·0001	1·36 (–0·2 to 2·8)	–0·49 (–1·9 to 1·1)	<0·0001
Appendicular LBM (LBM of arms and legs)	0·87 (–0·1 to 1·7)	0·30 (–0·9 to 1·1)	<0·0001	0·62 (0·2 to 1·4)	–0·21 (–1·1 to 0·5)	<0·0001
LBM of arms only	0·23 (–0·1 to 0·5)	0·01 (–0·3 to 0·3)	<0·0001	0·17 (–0·07 to 0·5)	–0·04 (–0·3 to 0·1)	<0·0001

Data are median (IQR). LBM=lean body mass. *Additional body composition parameters were measured via dual energy X-ray absorptiometry as specified per protocols at the same time LBM was assessed. Data for these additional body composition parameters were summarised by treatment group as a post-hoc exploratory analysis. Change from baseline to week 12 in LBM is shown only for comparison to the other body composition parameters at this timepoint.

Table 3: **Post-hoc analysis of changes in additional body composition parameters (kg)* from baseline to week 12**

	ROMANA 1						ROMANA 2					
	Anamorelin (n=320)			Placebo (n=161)			Anamorelin (n=330)			Placebo (n=161)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
Metabolism and nutrition disorders	17 (5%)	2 (1%)	0	8 (5%)	1 (1%)	0	14 (4%)	6 (2%)	1 (<1%)	2 (1%)	0	0
Diabetes, including inadequate control*	3 (<1%)	0	0	3 (2%)	1 (1%)	0	5 (2%)	2 (<1%)	0	0	0	0
Hyperglycaemia	16 (5%)	1 (<1%)	0	5 (3%)	0	0	10 (3%)	4 (1%)	0	1 (1%)	0	0
Hypertriglyceridaemia	0	0	0	0	0	0	0	0	1 (<1%)	0	0	0
Hypocalcaemia	0	1 (<1%)	0	0	0	0	0	0	0	0	0	0
Investigations	6 (2%)	0	0	4 (2%)	1 (1%)	0	3 (1%)	1 (<1%)	0	2 (1%)	1 (1%)	0
Blood glucose increased	0	0	0	0	0	0	0	1 (<1%)	0	0	0	0
γ-glutamyltransferase increased	0	0	0	0	0	0	0	0	0	0	1 (1%)	0
Neutrophil count decreased	1 (<1%)	0	0	0	1 (1%)	0	0	0	0	0	0	0
Gastrointestinal disorders	20 (6%)	0	0	3 (2%)	0	0	5 (2%)	1 (<1%)	0	3 (2%)	3 (2%)	0
Constipation	1 (<1%)	0	0	0	0	0	1 (<1%)	0	0	0	1 (1%)	0
Nausea	12 (4%)	0	0	1 (<1%)	0	0	4 (1%)	1 (<1%)	0	2 (1%)	1 (1%)	0
Vomiting	2 (1%)	0	0	0	0	0	0	1 (<1%)	0	1 (1%)	1 (1%)	0
Skin and subcutaneous tissue disorders	2 (1%)	0	0	2 (1%)	0	0	1 (<1%)	1 (<1%)	0	1 (1%)	0	0
Rash	0	0	0	1 (1%)	0	0	0	1 (<1%)	0	0	0	0
Cardiac disorders	0	0	1 (<1%)	0	0	0	1 (<1%)	0	0	0	0	0
Ischaemic cardiomyopathy	0	0	1 (<1%)	0	0	0	0	0	0	0	0	0

Data are n (%). Table displays all drug-related treatment-emergent adverse events of grades 1–2 with 10% incidence or higher in either group plus any grades 3–4 within the safety population; there were no treatment-related deaths in either study. Treatment-emergent events are defined as adverse events beginning on or after first dose and through the 7-day post-dose window, or events that start before first dose, but worsen during treatment or through the 7-day window after last dose. If a patient had more than one adverse event within a preferred term, the patient was counted only once in that preferred term at the worst CTCAE grade. CTCAE=Common Terminology Criteria for Adverse Events. *Event category includes events of diabetes mellitus, diabetes mellitus inadequate control, and type 2 diabetes mellitus.

Table 4: **Summary of drug-related treatment-emergent adverse events**

ROMANA 2 studies (figure 2). In subgroup analysis of the median of the change in handgrip strength from baseline over 12 weeks, men in ROMANA 1 were the only subgroup with a statistically significant treatment difference between anamorelin (–0·76 kg [95% CI –1·56 to –0·11]) and placebo (–2·51 [–3·96 to –1·37], p=0·024). The rest of the subgroup analyses are not shown.

Patients assigned to anamorelin had a significantly greater mean increase in bodyweight over 12 weeks than did patients assigned to placebo in both studies (table 2), with significant differences noted at week 3 (p<0·0001) that were sustained throughout the study period (figure 3A). Data from a post-hoc analysis showed that patients taking anamorelin also had a significantly greater median increase in additional measures of body composition including total body mass, fat mass, and appendicular lean body mass from baseline to week 12 than did those taking placebo (table 3). The association between gains in arm lean body mass and change in handgrip strength was also assessed on a post-hoc basis.

Although there was a reasonable correlation between baseline upper limb appendicular lean body mass and handgrip strength in all groups (r^2=0·65), there was no correlation between changes in either variable at 12 weeks (appendix p 13).

Patients assigned to anamorelin had a significant improvement in their mean anorexia–cachexia symptoms from baseline over 12 weeks compared with patients assigned to placebo in ROMANA 1 and ROMANA 2 (table 2), with significant differences in symptoms noted at week 3 and sustained throughout the study (figure 3B). Differences in the individual items of the anorexia–cachexia scale between treatment groups at week 12 are shown in the appendix. Patients in ROMANA 1 had improvement in their fatigue symptoms at weeks 9 and 12 (figure 3C); however, fatigue scores were not significantly different between treatment groups over the 12-week study period (table 2).

Median survival over 1 year, pooled for both trials, showed no difference between study groups (8·90 months [95% CI 8·3–9·8] for anamorelin *vs* 9·17 months [7·9–11·0] for placebo); hazard ratio 1·06, 95% CI 0·89–1·26; p=0·47). Additionally, each study population was individually assessed and results also showed no difference in survival between treatment groups (data not shown). 582 events (deaths) occurred within the 12-month follow-up in the pooled analysis from 979 patients.

Table 4 shows treatment-related adverse events with a 10% or higher incidence of grade 1 or 2 events or any grade 3 or 4 events in either study. There were no treatment-related deaths. The most common treatment-related adverse events were diabetes and hyperglycaemia, although the difference between treatment groups was less than five percentage points. The next most common treatment-related adverse event was gastrointestinal disorders due to grade 1 or 2 nausea (table 4). Of note, the incidence of treatment-emergent grade 1–2 oedema was low in both studies, and generally similar between anamorelin and placebo groups (21 of 320 [7%] patients *vs* nine of 161 [6%] patients in ROMANA 1; 13 of 330 [4%] patients *vs* three of 161 [2%] patients in ROMANA 2). The incidence of patients who discontinued for drug-related treatment-emergent adverse events was low in both the anamorelin and placebo groups (two of 320 [<1%] patients *vs* 0 of 161 patients respectively in ROMANA 1; two of 330 [<1%] patients *vs* two [1%] of 161 patients, respectively in ROMANA 2). No patients had dose reductions. Because patients received a variety of concomitant cytotoxic chemotherapy regimens, which confounds interpretation of low-frequency events, no statistical comparisons were made in the number of adverse events.

Discussion

Findings from these two phase 3 studies show that anamorelin significantly improves lean body mass, but not handgrip strength, in patients with advanced non-small-cell lung cancer. Most participants in the trials had metastatic disease and were receiving chemotherapy, which is a population known to experience substantial cachexia-related weight loss. The increase in patients' weight with anamorelin was early and progressive, with significant differences emerging as early as 3 weeks. Patients assigned to anamorelin also had a rapid and sustained improvement in their anorexia and cachexia symptoms. In a debilitated population, such a rapid attenuation of cachexia and associated symptoms is clinically important, especially in patients with a short survival.

These results are in contrast to those seen with the commonly prescribed drugs for anorexia and cachexia—namely corticosteroids and progestational drugs, which increase only appetite and bodyweight.[18,32,33] Importantly, although cross-trial comparisons must be made with caution, the median gain in lean body mass for patients assigned to anamorelin was greater than the results reported in cancer survivors who participated in resistance-based exercise programmes.[19,20] Thus, anamorelin has independent potential to treat loss of lean body mass in patients with advanced cancer and cachexia and could act as an adjunct to exercise. The increases in lean body mass, as well as bodyweight, are also important because previous studies have shown that body image dissatisfaction is strongly associated with patients' weight loss and with psychosocial distress in both patients and their caregivers.[21] Subgroup analysis showed that anamorelin had a significant effect on lean body mass compared with placebo for most of the subgroups in both studies.

We noted no difference between treatment groups in handgrip strength changes in either study, or in any subgroups, except for men in ROMANA 1. Previous phase 1 studies have shown similar pharmacodynamic responses between men and women, whereby the magnitude of growth hormone response after oral dosing was almost identical, showing an absence of gender effect.[22]

The absence of concordance between the observed changes in lean body mass and handgrip strength might be due to several factors that lead to an increase in lean body mass, but no change in the contractile mass of protein in skeletal muscle. One possible explanation is that the increase in lean body mass might have been secondary to an expansion of the extracellular water space. However, the rate of oedema reported in patients assigned to anamorelin was low, and fluid retention is not a known action of ghrelin. Another possibility is that ascites, pleural effusions, or increased tumour mass accounted for the rise in lean body mass. However, about half of the gain in lean body mass was due to an increase in appendicular lean body mass, mainly skeletal muscle, which would not be affected by physiological changes in the chest or abdomen, and increases in lean body mass in the arms were also significant in both studies.

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Moreover, there was no evidence of tumour growth stimulation, as shown by similar overall survival between study groups. Other possible explanations include the measurement of body composition by DXA scanning, which estimates tissue volume rather than specific composition. Thus, whether the structural protein or glycogen content of the patients' muscles was altered is not known. However, to determine changes in muscle content would require a biopsy or alternative diagnostic techniques that were not part of these studies. Importantly, evidence from animal models of cancer cachexia and in-vitro systems show that ghrelin can drive preservation of muscle mass and structural protein even in the presence of platinum chemotherapy.[23]

Previous data also suggest that the linear correlation between muscle mass and strength might be abnormal in individuals with systemic inflammation and chronic illness.[24–26] The prevalence of systemic inflammation ranges from 40% to 60% in patients with non-small-cell lung cancer, and many patients with lung cancer have concomitant chronic illness that contributes to their inflammatory state. At baseline, roughly two-thirds of study participants had evidence of systemic inflammation based on increased C-reactive protein concentrations (table 1). We noted no difference in the changes of handgrip strength between treatment groups. Phase 2 studies[13,15] with anamorelin have also showed inconsistency in terms of statistical significance. Together, these findings suggest that there is a high degree of variability in handgrip strength results across studies. Other phase 3 studies have included indices of lower-limb strength or power and have shown similar variability.[27] Thus, the most appropriate measure of muscle strength in patients with advanced cancer is unknown, as is the magnitude of lean body mass increase that might be needed to achieve a detectable change in muscle strength in this patient population.

Patients receiving anamorelin had significant and clinically meaningful improvements in symptom burden, including symptoms related to loss of appetite and food intake, compared with those assigned to placebo. Although a placebo effect was observed in these studies, this finding is consistent with previously published work showing that patients assigned to placebo often report improvement in their symptoms.[28] However, after a brief initial improvement in both study groups, patients assigned to placebo had worsening of these symptoms, whereas the benefit was sustained in patients receiving anamorelin. The significant increase in both total body and fat mass in patients receiving anamorelin in both trials suggests that the improvement in anorexia symptoms was physiologically meaningful and probably led to increased food intake.

Although patients assigned to anamorelin in ROMANA 1 had a significant improvement in fatigue in the final weeks of the study period, similar results were not seen in ROMANA 2. However, baseline differences between the study populations, including a greater number of study participants with ECOG performance status of 2 and a lower mean BMI and lean body mass in ROMANA 2, suggest that the patient sample in ROMANA 2 was a slightly different population. Cancer-related fatigue is a difficult symptom to ameliorate in patients with advanced cancer, especially in those with more symptomatic disease, unless the underlying disease can be reversed.[29] Thus, more research is needed to determine the effect of anamorelin on fatigue.

Despite the fact that most study participants were receiving chemotherapy, radiotherapy, or both, treatment-related adverse events were low in both study groups. It is important that improvement of cachexia outcomes such as lean body mass, weight, and anorexia does not come at the cost of increased side-effects or toxic effects. These phase 3 studies show that anamorelin was well tolerated in patients with advanced non-small-cell lung cancer. Importantly, despite the variability in the clinical and cancer characteristics of the patients, there was no difference in overall survival between treatment groups. Although data for the role of growth hormone and IGF-1 in carcinogenesis are conflicting, these studies show that anamorelin does not negatively affect survival, which is consistent with findings from previous phase 2 trials, as well as animal studies with anamorelin.[13,15,30] Thus, anamorelin represents a well-tolerated medicine that can be safely given during cancer treatment.

These two studies have several limitations. First, we did not show improvements in handgrip strength with anamorelin, which was the co-primary endpoint. Second, although our patient-reported measures and exploratory endpoints suggest that patients had increased food intake with anamorelin, we did not measure study participants' caloric intake or collect food diaries. Third, although we present data on pooled overall survival, study participants were permitted to receive any standard chemotherapy or radiotherapy, and not all had follow-up radiographic imaging, making it difficult to assess the effect of anamorelin on cancer outcomes such as tumour response rates. Fourth, assessments of changes in lean body mass and handgrip strength within additional subgroups of interest (including by inflammatory status, weight loss grades, and chemotherapy regimens) were not done, but do represent areas of future research. Additionally, the issue of when an individual is refractory to intervention is clearly very important and is also an area of future research. Finally, as is common in studies of patients with advanced non-small-cell lung cancer, there was substantial attrition due to worsening health status and death, with 117 (12%) of 979 study participants deceased by week 12. To address this issue, we used alternative analysis methods for the primary and secondary endpoints, including multiple imputation with ranking and pattern mixture repeated measures models, respectively. Since death is an expected outcome of the study, we included death as part of the treatment

comparison of the primary analysis of lean body mass and handgrip strength. As significant differences in ranks could be due to a survival advantage or a change in the primary endpoint, we also did post-hoc analysis on lean body mass and handgrip strength values for only patients who did not die during the studies (appendix p 6–12). Although these data confirm the positive improvement in lean body mass over 12 weeks with anamorelin treatment, this post-hoc analysis is biased by only using alive-patient data. Nevertheless, it does emphasise that type of analysis and handling of death makes no gross difference to the primary outcome.

In conclusion, in patients with advanced non-small-cell lung cancer and cachexia receiving a variety of different cancer-direct treatments, anamorelin improved lean body mass, bodyweight, fat mass, and symptom burden compared with placebo. These anabolic and orexigenic benefits are consistent with anamorelin's mechanism of action as a ghrelin-receptor agonist. The absence of a detectable change in handgrip strength in these studies, despite the significant increase in lean body mass, is consistent with previous studies. Anamorelin represents a safe and effective treatment option for patients with anorexia and cachexia.

Contributors

JST, KCF, DCC, APA, and JF were involved in the study design. JF, YY, and EMD collected and analysed the data in conjunction with the authors, all of whom had full access to all data. The manuscript was written by JST, and was reviewed, modified, and approved in its final version by all of the authors. All authors vouch for the accuracy and completeness of the data reported and the fidelity of the studies to the protocols.

Declaration of interests

APA is an employee of Flatiron Health, serves on the Board of Directors at Athenahealth, is a consultant for Bristol-Myers Squibb and Helsinn Therapeutics and has received honorarium from Bristol-Myers Squibb and Roche/Genentech. DCC is an unpaid advisory board member of Helsinn Pharmaceuticals, has received an unrestricted research grant from Mundipharma, and is a consultant for Mayne Pharma. EMD, JF, and YY are employees of Helsinn Therapeutics (US). KCF has received lecture fees and is a paid advisory board member of Helsinn Pharmaceuticals. JST reports receipt of travel funds from Helsinn Therapeutics.

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