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Ponsegromab for the Treatment of Cancer Cachexia

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ABSTRACT

BACKGROUND

Cachexia is a common complication of cancer and is associated with an increased risk of death. The level of growth differentiation factor 15 (GDF-15), a circulating cytokine, is elevated in cancer cachexia. In a small, open-label, phase 1b study involving patients with cancer cachexia, ponsegromab, a humanized monoclonal antibody inhibiting GDF-15, was associated with improved weight, appetite, and physical activity, along with suppressed serum GDF-15 levels.

METHODS

In this phase 2, randomized, double-blind, 12-week trial, we assigned patients with cancer cachexia and an elevated serum GDF-15 level (≥1500 pg per milliliter) in a 1:1:1:1 ratio to receive ponsegromab at a dose of 100 mg, 200 mg, or 400 mg or to receive placebo, administered subcutaneously every 4 weeks for three doses. The primary end point was the change from baseline in body weight at 12 weeks. Key secondary end points were appetite and cachexia symptoms, digital measures of physical activity, and safety.

RESULTS

A total of 187 patients underwent randomization. Of these patients, 40% had non–small-cell lung cancer, 32% had pancreatic cancer, and 29% had colorectal cancer. At 12 weeks, patients in the ponsegromab groups had significantly greater weight gain than those in the placebo group, with a median between-group difference of 1.22 kg (95% credible interval, 0.37 to 2.25) in the 100-mg group, 1.92 (95% credible interval, 0.92 to 2.97) in the 200-mg group, and 2.81 (95% credible interval, 1.55 to 4.08) in the 400-mg group. Improvements were observed across measures of appetite and cachexia symptoms, along with physical activity, in the 400-mg ponsegromab group relative to placebo. Adverse events of any cause were reported in 70% of the patients in the ponsegromab group and in 80% of those in the placebo group.

CONCLUSIONS

Among patients with cancer cachexia and elevated GDF-15 levels, the inhibition of GDF-15 with ponsegromab resulted in increased weight gain and overall activity level and reduced cachexia symptoms, findings that confirmed the role of GDF-15 as a driver of cachexia. (Funded by Pfizer; ClinicalTrials.gov number, NCT05546476.)

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Cachexia (wasting syndrome) is prevalent among patients with multiple forms of cancer[1] and can lead to weight loss, muscle wasting, reduced quality of life, functional impairment, and reduced survival.[2] International consensus criteria define this multifactorial syndrome as a weight loss of more than 5% during a 6-month period or weight loss of more than 2% in patients with either a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of less than 20 or sarcopenia.[2] With no approval of medications for the treatment of cancer cachexia in the United States or Europe, pharmacologic options are limited.

A recent guideline supports low-dose olanzapine to improve appetite and weight in patients with advanced cancer,[3] a recommendation that is largely based on a single-center study.[4] Otherwise, short-term trials of a progesterone analogue or glucocorticoids offer the potential for limited benefits at the risk of unfavorable side effects (e.g., thromboembolic events with the use of progestins).[3,5,6] Clinical trials of other agents have not shown benefits sufficient for regulatory approval.[7-9] Although anamorelin, a ghrelin receptor agonist, is approved in Japan for the treatment of cancer cachexia,[5] the drug resulted in modest increases in body composition without an improvement in hand-grip strength[9] and ultimately was not approved by the Food and Drug Administration. Safe, effective, and targeted therapies for cancer cachexia are needed.[10,11]

Growth differentiation factor 15 (GDF-15) is a stress-induced cytokine that binds to the glial cell–derived neurotrophic factor family receptor alpha-like protein (GFRAL) in the hindbrain.[12] The GDF-15–GFRAL pathway has emerged as a main modulator of anorexia and body-weight regulation and is implicated in the pathogenesis of cachexia.[13] In animal models, GDF-15 induced a cachexia phenotype, and GDF-15 inhibition alleviated this phenotype.[14-16] Furthermore, elevated GDF-15 levels are associated with loss of weight and skeletal muscle mass along with reduced strength and survival in patients with cancer,[17,18] factors that highlight GDF-15 as a potential therapeutic target.

Ponsegromab (PF-06946860) is a potent, highly selective, humanized monoclonal antibody that binds to circulating GDF-15, thereby inhibiting the interaction with its GFRAL receptor. In a small, open-label, phase 1b study involving 10 patients with cancer cachexia who had elevated circulating GDF-15 levels, ponsegromab was associated with improved weight, appetite, and physical activity, along with suppressed serum GDF-15 levels, with a low frequency of adverse events.[19] We conducted a phase 2 trial to assess the safety and efficacy of ponsegromab, as compared with placebo, in patients with cancer cachexia who had elevated circulating GDF-15 levels to test the hypothesis that GDF-15 is a main mechanistic driver of this condition.

Methods

Trial Design and Oversight

This randomized, double-blind, placebo-controlled, dose-ranging trial was conducted at 74 sites in 11 countries. The trial design, which was published previously,[20] called for a 12-week double-blind phase (Part A), followed by an optional open-label extension (Part B). Here, we report the results of Part A only, because Part B is ongoing.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol (available with the full text of this article at NEJM.org) was approved by the independent ethics committee or institutional review board at each site. The trial was designed by the sponsor (Pfizer) in collaboration with the executive committee. The sponsor and investigators were responsible for data collection. The sponsor performed site monitoring and data analysis according to a predefined statistical analysis plan. The first author wrote the first draft of the manuscript. All the coauthors reviewed the first draft and contributed to all subsequent drafts. No one who is not an author contributed to the writing of the manuscript. All the authors had full access to trial data, contributed to the interpretation of the data, and approved the submission of the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

Eligible patients were adults (≥18 years of age) with cancer (non–small-cell lung cancer, pancreatic cancer, or colorectal cancer), cachexia (defined by an involuntary weight loss of >5% within the previous 6 months or of >2% with a BMI of <20,

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as included in the international consensus definition of cachexia[2]), a serum GDF-15 level of at least 1500 pg per milliliter, an Eastern Cooperative Oncology Group performance-status score of 3 or less (on a scale ranging from 0 to 5, with higher numbers reflecting greater disability), and a life expectancy of at least 4 months. Key exclusion criteria were cachexia caused by a nonmalignant illness, planned surgery, and the use of drugs prescribed to increase weight or appetite. A full list of eligibility criteria is provided in the Supplementary Appendix, available at NEJM.org.

INTERVENTIONS AND PROCEDURES

Patients were randomly assigned in a 1:1:1:1 ratio to receive ponsegromab at a dose of 100 mg, 200 mg, or 400 mg or to receive placebo, administered subcutaneously every 4 weeks for three doses (Fig. S1 in the Supplementary Appendix). Randomization was performed by means of an interactive Web-based response system, stratified according to receipt or nonreceipt of concomitant platinum-based chemotherapy, given the potential of such therapy to increase the GDF-15 level.[21]

END POINTS AND ASSESSMENTS

The primary end point was the change from baseline in body weight at 12 weeks. Key secondary end points were the change from baseline in the score on the Functional Assessment of Anorexia Cachexia Treatment–Anorexia Cachexia Subscale (FAACT-ACS), which ranges from 0 to 48, with higher scores indicating a better outcome and a 4-point increase identified as a response;[22,23] the score on the FAACT 5-Item Anorexia Symptom Scale (FAACT-5IASS), which ranges from 0 to 20, with higher scores indicating a better outcome and a 2-point increase identified as a response[22] (Fig. S2); and the score on the sponsor-developed Cancer Related Cachexia Symptom Diary, which measures the severity of appetite loss, nausea, and fatigue on a 0 to 10 scale, along with vomiting frequency, during a 24-hour period (Fig. S3). Additional secondary end points included the change from baseline in physical activity and gait end points, as measured with the use of wearable digital health devices (ActiGraph CentrePoint Insight Watches). Minimum wear-time requirements were prespecified. Safety assessments included the number of adverse events during treatment, results on laboratory testing, vital signs, and electrocardiograms.

Exploratory end points included the change from baseline in the lumbar skeletal muscle index (calculated as the skeletal muscle area divided by the square of the height), which correlates with whole-body skeletal muscle.[24] Computed tomography (CT) imaging of the chest, abdomen, and pelvis were performed before randomization and at 12 weeks. A central imaging laboratory assessed skeletal muscle area at the level of the third lumbar vertebrae in a blinded manner. Site-based assessment of tumor response was based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[25] We measured screening serum GDF-15 levels using the Roche Elecsys GDF-15 assay.[26] During treatment, unbound GDF-15 levels were measured with the use of a sponsor-developed electrochemiluminescence assay. We used the Patient Global Impression of Severity instrument to assess the severity of appetite loss at baseline (Fig. S4).

STATISTICAL ANALYSIS

We determined that a sample size of 168 patients would provide the trial with approximately 80% power for assessing the primary end point, using Bayesian methods that included an informative prior (based on historical results from relevant internal and external studies) of the placebo change from baseline at 12 weeks. (Details regarding the statistical methods are provided in the Supplementary Appendix.) The safety population included all the patients who had received at least one dose of ponsegromab or placebo. A post hoc Bayesian analysis was performed to calculate efficacy end points with the use of a treatment-policy estimand (based on a modified intention-to-treat principle including all the patients who had received at least one dose of ponsegromab or placebo) that included all observations, regardless of the occurrence of an intercurrent event, for alignment with the prespecified analysis of the primary end point, which was based on Bayesian inferential principles.

The primary end point was analyzed with the use of a Bayesian hierarchical Emax model that included the informative placebo prior, applied to week 12 results from a Bayesian joint longitudinal analysis, including all time points up to 12 weeks, after adjustment for the competing risk of death and treatment policy for other intercurrent events, such as treatment discontinuation. The primary end point was also analyzed in a similar

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=45)	Ponsegromab, 100 mg (N=46)	Ponsegromab, 200 mg (N=46)	Ponsegromab, 400 mg (N=50)	All Patients (N=187)
Median age (IQR) — yr	66 (57–71)	73 (64–76)	66 (60–72)	67 (60–72)	67 (60–74)
Female sex — no. (%)	17 (38)	19 (41)	15 (33)	18 (36)	69 (37)
Race — no. %†					
White	26 (58)	27 (59)	28 (61)	35 (70)	116 (62)
Asian	18 (40)	19 (41)	18 (39)	15 (30)	70 (37)
Not reported	1 (2)	0	0	0	1 (1)
Median weight (IQR) — kg	53.8 (46.0–58.4)	50.2 (43.4–61.2)	55.2 (47.0–69.5)	58.1 (50.9–67.4)	54.8 (46.0–63.8)
Body-mass index					
Median (IQR)	19.0 (17.2–21.3)	19.3 (17.5–21.2)	20.6 (17.7–24.1)	20.5 (19.2–22.8)	19.8 (17.6–22.3)
<20 — no. (%)	30 (67)	28 (61)	22 (48)	19 (38)	99 (53)
Percent weight loss during 6 mo before screening — no. (%)					
<5%	6 (13)	10 (22)	9 (20)	5 (10)	30 (16)
5 to <10%	21 (47)	15 (33)	12 (26)	21 (42)	69 (37)
≥10%	18 (40)	21 (46)	25 (54)	24 (48)	88 (47)
BMI-adjusted weight-loss category‡					
No. of patients (%)					
Category 1	0	0	1 (2)	1 (2)	2 (1)
Category 2	0	6 (13)	3 (7)	5 (10)	14 (7)
Category 3	15 (33)	18 (39)	24 (52)	20 (40)	77 (41)
Category 4	30 (67)	22 (48)	18 (39)	24 (48)	94 (50)
Median category (IQR)	4 (3–4)	3 (3–4)	3 (3–4)	3 (3–4)	4 (3–4)
Cancer type — no. (%)					
Non–small-cell lung	15 (33)	17 (37)	21 (46)	21 (42)	74 (40)
Pancreatic	14 (31)	16 (35)	15 (33)	14 (28)	59 (32)
Colorectal	16 (36)	13 (28)	10 (22)	15 (30)	54 (29)
Cancer stage — no. (%)					
I	0	1 (2)	0	1 (2)	2 (1)
II	3 (7)	5 (11)	4 (9)	2 (4)	14 (7)
III	12 (27)	10 (22)	8 (17)	4 (8)	34 (18)
IV	30 (67)	30 (65)	34 (74)	43 (86)	137 (73)
Median interval from cancer diagnosis to randomization (IQR) — mo	15.3 (4.6–33.7)	10.6 (3.2–24.0)	10.9 (3.5–21.7)	11.2 (4.8–24.3)	11.7 (4.0–26.4)
Receipt of systemic anticancer therapy — no. (%)§					
Any	42 (93)	42 (91)	41 (89)	43 (86)	168 (90)
Platinum-based	17 (38)	15 (33)	18 (39)	18 (36)	68 (36)

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Table 1. (Continued.)

Characteristic	Placebo (N=45)	Ponsegromab, 100 mg (N=46)	Ponsegromab, 200 mg (N=46)	Ponsegromab, 400 mg (N=50)	All Patients (N=187)
Line of systemic anticancer therapy — no. (%)¶					
0	1 (2)	2 (4)	2 (4)	4 (8)	9 (5)
1	17 (38)	25 (54)	20 (43)	20 (40)	82 (44)
2	13 (29)	7 (15)	10 (22)	15 (30)	45 (24)
3	9 (20)	3 (7)	7 (15)	3 (6)	22 (12)
≥4	5 (11)	8 (17)	7 (15)	8 (16)	28 (15)
Missing data	0	1 (2)	0	0	1 (1)
Median serum GDF-15 level (IQR) — pg/ml	3770 (2594–7667)	3507 (2310–6134)	4221 (2290–8623)	4905 (2123–7709)	3903 (2366–7677)
ECOG performance-status score — no. (%)					
0	10 (22)	8 (17)	9 (20)	6 (12)	33 (18)
1	27 (60)	27 (59)	30 (65)	39 (78)	123 (66)
2	7 (16)	9 (20)	6 (13)	5 (10)	27 (14)
3	1 (2)	2 (4)	1 (2)	0	4 (2)

* Percentages may not total 100 because of rounding. BMI denotes body-mass index, and IQR interquartile range.
† Race was reported by the patients.
‡ The BMI-adjusted weight-loss category is determined on a scale of 0 to 4, with grade 4 indicating more refractory cachexia and shortest survival. This category was determined according to the percentage of weight loss in the 6 months before the screening visit and the BMI at screening.
§ Data are listed for all cancer therapies that were being administered 28 days before until 28 days after randomization.
¶ This category includes all current and previous lines of systemic anticancer therapy.

manner with the use of an on-treatment estimand in which all observations that were made after an intercurrent event were censored. In post hoc analyses of other end points and subgroups, we used similar Bayesian analysis of covariance or joint longitudinal analyses, as appropriate. The protocol prespecified primary analysis of the primary end point that was based on an on-treatment estimand used a similar approach but with the Bayesian Emax model applied to week 12 results from a frequentist mixed model repeated measures (MMRM) analysis. The results of the post hoc analyses are presented here, and the methods and results of all prespecified analyses are provided in the Supplementary Appendix.

Analysis results are accompanied by 95% credible intervals or confidence intervals, as appropriate. Significance for the primary analysis was predefined as a one-sided posterior probability less than 0.05. No multiplicity adjustments were made for this phase 2 trial; therefore, credible or confidence intervals should not be used in place of hypothesis testing. Additional details regarding the statistical methods are provided in the Supplementary Appendix and the statistical analysis plan.

RESULTS

PATIENTS

From February through December 2023, a total of 187 patients underwent randomization to receive ponsegromab at a dose of 100 mg (46 patients), a dose of 200 mg (46 patients), or a dose of 400 mg (50 patients) or to receive placebo (45 patients). Of these patients, 74 (40%) had non–small-cell lung cancer, 59 (32%) had pancreatic cancer, and 54 (29%) had colorectal cancer. All 187 patients were treated, and 137 (73%) completed the week 12 visit, with similar frequencies of early discontinuation across groups (Fig. S5).

The demographic and clinical characteristics of the patients were generally balanced across

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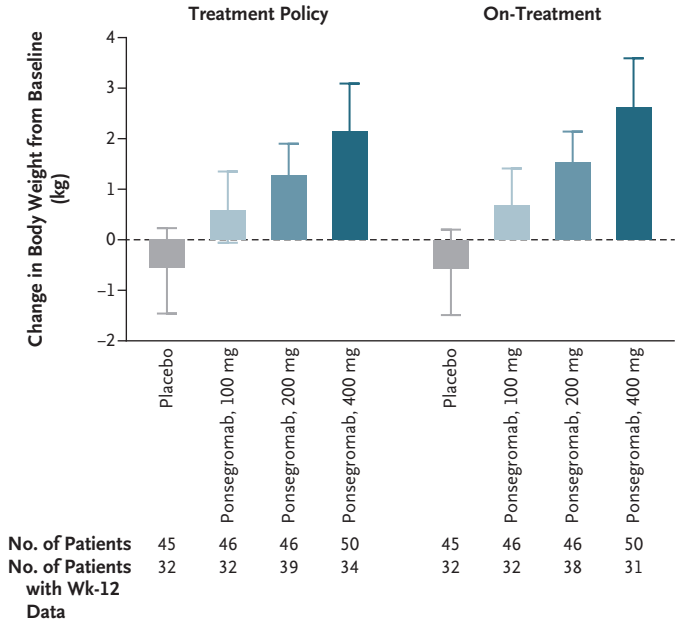

Figure 1. Change from Baseline in Body Weight at 12 Weeks.

Shown is the primary end point (the change in weight from baseline to 12 weeks) among patients with cancer cachexia in the ponsegromab groups and the placebo group. The primary end point was analyzed with the use of a hierarchical Emax model applied to week 12 results from a Bayesian joint longitudinal analysis, after adjustment for the competing risk of death and treatment policy for other intercurrent events, such as treatment discontinuation (in graph at left). The primary end point was also analyzed in a similar manner with the use of an on-treatment estimand in which all observations that were made after an intercurrent event were censored (in graph at right). No multiplicity adjustments were made, and credible intervals (indicated by I bars) should not be used in place of hypothesis testing.

groups (Table 1 and Tables S1 and S2). The median age was 67 years (interquartile range, 60 to 74), and 37% were women; 62% were White, and 37% were Asian, with underrepresentation of Black patients. The median weight was 54.8 kg (interquartile range, 46.0 to 63.8). The median interval from cancer diagnosis to randomization was 11.7 months (interquartile range, 4.0 to 26.4). The highest proportion of patients with stage IV disease in any cancer type was in the ponsegromab 400-mg group (86%, as compared with 65 to 74% in the other three groups). Most of the patients (90%) were receiving systemic anticancer therapies at the time of randomization. Overall, 36% of the patients were receiving platinum-based chemotherapy. The percentage of patients who were receiving palliative care was similar across trial groups. The median serum GDF-15 level was 3903 pg per milliliter (interquartile range, 2366 to 7677). The level of inflammation at baseline was similar across groups (Table S3).

CHANGE IN BODY WEIGHT

According to the post hoc Bayesian analysis, the increase in weight from baseline in all three ponsegromab groups was significant as compared with the placebo group at 12 weeks. The between-group difference was 1.22 kg (95% credible interval, 0.37 to 2.25; posterior probability, <0.05) in the 100-mg group, 1.92 kg (95% credible interval, 0.92 to 2.97; posterior probability, <0.05) in the 200-mg group, and 2.81 kg (95% credible interval, 1.55 to 4.08; posterior probability, <0.05) in the 400-mg group (Fig. 1 and Table S4). The effect of ponsegromab on weight was consistent across various sensitivity analyses, including the post hoc Bayesian Emax analyses with the on-treatment estimand (Fig. 1), and with the incorporation of a vague prior for the placebo change from baseline at 12 weeks (Table S5). The effect was also similar in the prepecified Bayesian Emax analyses with the on-treatment estimand with the incorporation of both informative and vague placebo priors and with the treatment-policy estimand (Fig. S6 and Tables S6 and S7). Supplementary analysis showed an estimated difference with placebo in the mean percent change from baseline in body weight at week 12 of 2.21 percentage points (95% credible interval, −0.20 to 4.46) in the 100-mg group, 2.99 percentage points (95% credible interval, 0.64 to 5.35) in the 200-mg group, and 5.46 percentage points (95% credible interval, 3.05 to 7.87) in the 400-mg group. Greater weight gain was observed in all the ponsegromab groups than in the placebo group at week 8 (Tables S8 and S9).

The effect of 400 mg of ponsegromab on weight was consistent across key subgroups, including cancer type, quartile of serum GDF-15 level, platinum chemotherapy exposure, BMI, and baseline systemic inflammation as assessed by either the ratio of C-reactive protein to albumin[27] or by the modified Glasgow Prognostic Score[28] (Fig. 2 and Fig. S7). Changes in weight were consistent with GDF-15 suppression at 12 weeks, with a median factor change from baseline in the unbound GDF-15 level of 0.15 (interquartile range, 0.03 to 1.02) in the 100-mg group, 0.07 (interquartile range, 0.02 to 0.75) in the 200-mg group, and 0.02 (interquartile range,

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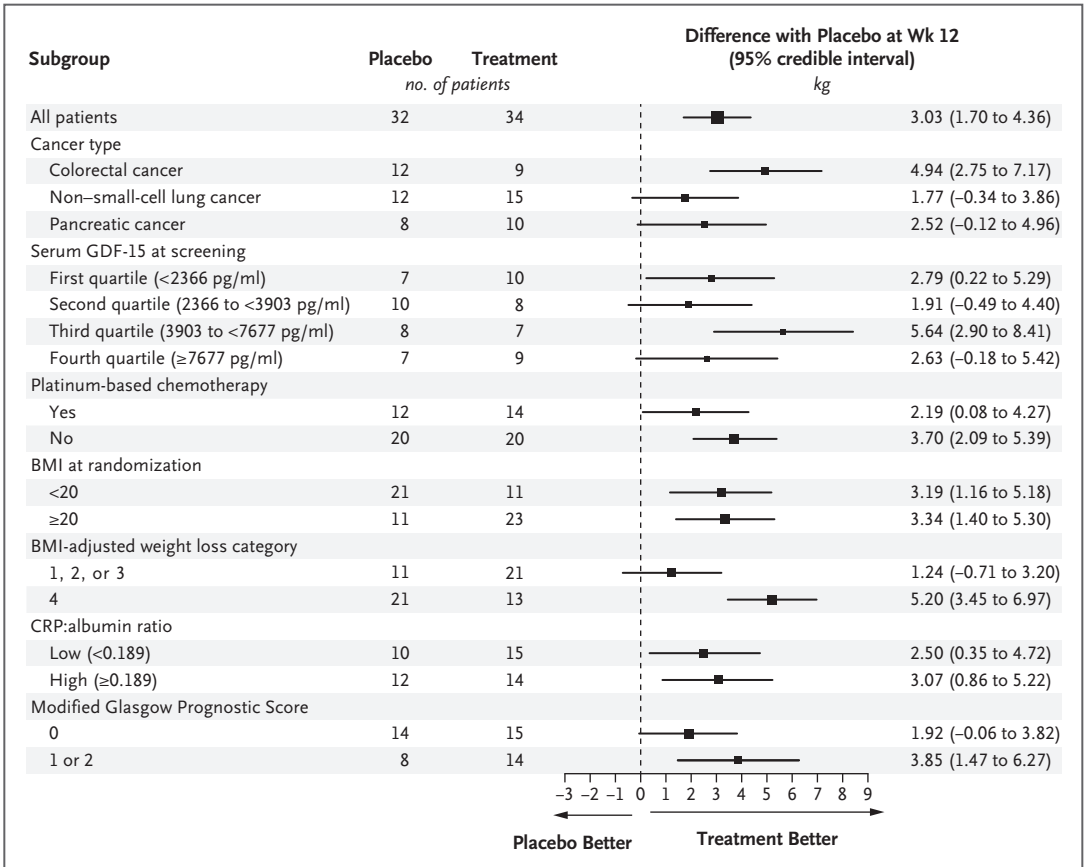

Figure 2. Subgroup Analysis of the Primary End Point in the 400-mg Ponsegromab Group.

The selection of key subgroups of interest was based on post hoc Bayesian joint longitudinal analyses after the adjustment for the competing risk of death on the basis of the treatment-policy estimand. No multiplicity adjustments were made, and credible intervals should not be used in place of hypothesis testing. BMI denotes body-mass index, CRP C-reactive protein, and GDF-15 growth differentiation factor 15.

0.02 to 0.04) in the 400-mg group, as compared with 1.02 (interquartile range, 0.74 to 1.40) in the placebo group.

PATIENT-REPORTED OUTCOMES AND PHYSICAL ACTIVITY

Among all the patients in the trial, a higher percentage of those in the 200-mg ponsegromab group (39%) reported no appetite loss at baseline than in the other groups (26% in the 100-mg group, 28% in the 400-mg group, and 21% in the placebo group) (Table S10). Patients in the 100-mg and 400-mg ponsegromab groups had improvements from baseline as compared with the placebo group at 12 weeks regarding scores on the FAACT-ACS (4.12 [95% credible interval, 0.86 to 7.34] and 4.50 [95% credible interval, 1.29 to 7.77], respectively) and the FAACT-5IASS (2.20 [95% credible interval, 0.36 to 3.99] and 2.39 [95% credible interval, 0.61 to 4.15], respectively) (Table 2). No material differences in the score on either the FAACT-ACS or FAACT-5IASS were observed in the 200-mg ponsegromab group relative to the placebo group.

Data regarding the change from baseline with respect to end points for physical activity and gait were available for 59 and 68 patients, respectively, owing to prespecified wear-time requirements and device issues. In this subgroup, patients in the 400-mg ponsegromab group had increased overall activity at 12 weeks as compared with the placebo group, with a difference of 72 minutes (95% credible interval, 37 to 107) per day with respect to nonsedentary physical activity (Table 2).

Findings from the prespecified analyses were similar to those of the post hoc analyses of the

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Table 2. Secondary End Points.*

End Point	Baseline		Change from Baseline at Week 12			
	N1†	Observed Mean	N2†	Observed Mean	Modeled Mean (95% Credible Interval)	Modeled Mean Difference from Placebo (95% Credible Interval)
Patient-reported outcome						
FAACT–Anorexia and Cachexia Subscale‡						
Placebo	42	27.5±7.9	30	0.5±8.3	0.57 (–1.64 to 2.79)	NA
Ponsegromab, 100 mg	43	27.3±7.8	27	5.5±7.2	4.68 (2.25 to 7.11)	4.12 (0.86 to 7.34)
Ponsegromab, 200 mg	41	28.4±9.2	33	1.2±10.1	1.30 (–1.02 to 3.49)	0.73 (–2.40 to 3.91)
Ponsegromab, 400 mg	47	27.0±9.3	30	4.2±5.8	5.07 (2.71 to 7.52)	4.50 (1.29 to 7.77)
FAACT–5-Item Anorexia Symptom Scale§						
Placebo	42	11.9±4.2	30	–0.2±4.5	0.22 (–1.02 to 1.45)	NA
Ponsegromab, 100 mg	43	11.0±3.9	27	3.1±4.2	2.43 (1.15 to 3.63)	2.20 (0.36 to 3.99)
Ponsegromab, 200 mg	41	12.2±5.2	33	–0.2±5.4	0.20 (–0.99 to 1.42)	–0.02 (–1.73 to 1.72)
Ponsegromab, 400 mg	47	11.0±4.8	30	2.5±3.7	2.62 (1.37 to 3.87)	2.39 (0.61 to 4.15)
Digital end point¶						
Nonsedentary physical activity — min/day						
Placebo	44	228.1±109.8	12	–29.9±100.5	–41.09 (–67.59 to –15.55)	NA
Ponsegromab, 100 mg	46	220.1±119.3	17	–13.9±58.8	–20.19 (–44.88 to 3.57)	20.89 (–15.49 to 57.25)
Ponsegromab, 200 mg	43	214.8±115.1	16	–27.0±38.7	–76.51 (–101.91 to –53.19)	–35.42 (–70.57 to 0.60)
Ponsegromab, 400 mg	46	243.7±104.1	14	31.6±75.5	30.61 (8.48 to 52.70)	71.70 (37.01 to 107.21)

* Plus–minus values are means ±SD. The listed analyses are based on post hoc Bayesian joint longitudinal analysis after adjustment for the competing risk of death. No adjustments for multiple comparisons were made, and credible intervals should not be used in place of hypothesis testing. NA denotes not applicable.

† N1 indicates the number of patients who underwent randomization and had available data at baseline; N2 indicates the number of patients who had available data regarding the change from baseline to week 12.

‡ Scores on the Functional Assessment of Anorexia Cachexia Treatment–Anorexia Cachexia Subscale (FAACT-ACS) range from 0 to 48, with higher scores indicating a lower burden of anorexia and cachexia symptoms.

§ Scores on the FAACT–5-Item Anorexia Symptom Scale (FAACT-5IASS) range from 0 to 20, with higher scores indicating a lower burden of anorexia symptoms.

¶ For end points derived from wrist sensors, patients were included in analyses for any given 7-day monitoring period if there were data for a minimum of 7 hours of awake wear time, 18 hours of total wear time per day for at least 3 days, or both.

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outcomes listed above (Table S11). At 12 weeks, no consistent differences between any ponsegromab group and the placebo group were seen regarding symptoms as assessed on the Cancer Related Cachexia Symptom Diary or in other physical-activity or gait end points (Tables S12 through S15).

CHANGE IN LUMBAR SKELETAL MUSCLE INDEX

The change in the lumbar skeletal muscle index, an exploratory end point, was calculated as the skeletal muscle area divided by the square of the height. In the 400-mg ponsegromab group, the difference from the placebo group in the increase in the lumbar skeletal muscle index was 2.04 cm^2 per square meter (95% credible interval, 0.27 to 3.83) at week 12 (Tables S16 and S17).

SAFETY

Similar percentages of patients in the ponsegromab and placebo groups reported adverse events of any cause (67 to 74% and 80%, respectively). The most common adverse events were diarrhea, cancer progression, anemia, hypokalemia, nausea, vomiting, and pyrexia, with patients in the placebo group reporting higher rates of diarrhea, nausea, and vomiting. Adverse events that were deemed by the investigator to be related to ponsegromab or placebo were reported in 4 to 11% of the patients in the ponsegromab groups and in 9% of those in the placebo group; most of the adverse events (88%) were mild to moderate.

Serious adverse events from any cause occurred in 22 to 40% of the patients in the ponsegromab groups and in 24% of those in the placebo group. No serious adverse event in the 400-mg ponsegromab group or the placebo group was considered to be related to ponsegromab or placebo by the investigator, whereas one serious adverse event in the 100-mg group (abdominal pain) and one in the 200-mg group (dyspnea) were considered to be trial related (Table 3 and Table S18).

There were 26 deaths during the trial period: 6 occurred in each of the 100-mg and 200-mg ponsegromab groups, 9 occurred in the 400-mg ponsegromab group, and 5 occurred in the placebo group. No deaths were considered to be trial related. The most frequent cause of death was progression of underlying cancer (in 16 patients [62%]), with the remaining 10 deaths (38%) due to adverse events (Table S19). Among the patients who died, the median time from the first dose until death was 40 to 70 days in the ponsegromab groups and 19 days in the placebo group. As compared with patients who completed the 12-week visit, those who died before that visit had a higher burden of stage IV disease (91% vs. 70%) and weight loss of at least 15% in the previous 6 months (48% vs. 20%) (Table S20).

No adverse trends were observed in laboratory or electrocardiographic findings (Tables S21 and S22). An increase in systolic blood pressure (difference with placebo, 9.6 mm Hg; 95% credible interval, 2.8 to 16.2) was observed in the 400-mg ponsegromab group at 12 weeks; no such difference was noted in the other ponsegromab groups (Tables S23 and S24), and no imbalances were observed according to categorical analysis (Table S25). Treatment-induced antidrug antibodies were detected in one patient in each of the 100-mg and 200-mg ponsegromab groups, without a substantial effect on circulating levels of ponsegromab or GDF-15. No adverse trends were observed in categories of overall tumor response according to RECIST criteria across groups (Table S26).

DISCUSSION

In this phase 2 trial involving patients with cancer cachexia and an elevated GDF-15 level, the inhibition of GDF-15 with ponsegromab resulted in a significant, robust increase in body weight at 12 weeks, as compared with placebo. In addition, patients in the ponsegromab groups had reduced cachexia symptoms and improved appetite, overall physical activity, and skeletal muscle mass. Differences in body weight relative to placebo were evident at 8 weeks after two doses of ponsegromab. In addition, all ponsegromab doses were considered to be safe and had a side-effect profile similar to that of placebo. Collectively, these results highlight the potential for ponsegromab as a targeted therapy for cancer cachexia.

Eligibility criteria permitted the enrollment of patients across three cancer types who were receiving any type or line of cancer treatment. The benefit of ponsegromab over placebo with respect to body weight was observed across all three cancer types. These results provide the first conclusive demonstration that GDF-15 is a common driver of cachexia across different malignant solid tumors, thereby establishing GDF-15 as a therapeutic target. Furthermore, elevated circulating

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Table 3. Adverse Events.*

Event	Placebo (N=45)	Ponsegromab, 100 mg (N=46)	Ponsegromab, 200 mg (N=46)	Ponsegromab, 400 mg (N=50)	Ponsegromab, Total (N=142)	All Patients (N=187)
Any cause						
Any adverse event — no. (%)	36 (80)	32 (70)	31 (67)	37 (74)	100 (70)	136 (73)
Total no. of adverse events	138	122	118	184	424	562
Grades 1–2	102	83	86	131	300	402
Grade 3	27	32	22	42	96	123
Grade 4	4	1	4	2	7	11
Death	5†	6‡	6‡	9‡	21	26
Serious adverse event						
Patients with event — no. (%)	11 (24)	15 (33)	10 (22)	20 (40)	45 (32)	56 (30)
No. of serious events	18	20	16	35	71	89
Patients with adverse event leading to discontinuation of ponsegromab or placebo — no. (%)	6 (13)	4 (9)	5 (11)	7 (14)	16 (11)	22 (12)
Adverse events reported in ≥7% of patients — no. (%)						
Diarrhea	8 (18)	3 (7)	4 (9)	5 (10)	12 (8)	20 (11)
Neoplasm progression	4 (9)	3 (7)	5 (11)	5 (10)	13 (9)	17 (9)
Anemia	5 (11)	4 (9)	4 (9)	4 (8)	12 (8)	17 (9)
Hypokalemia	4 (9)	6 (13)	0	6 (12)	12 (8)	16 (9)
Nausea	7 (16)	1 (2)	1 (2)	4 (8)	6 (4)	13 (7)
Vomiting	6 (13)	2 (4)	3 (7)	2 (4)	7 (5)	13 (7)
Pyrexia	3 (7)	0	5 (11)	5 (10)	10 (7)	13 (7)
Event related to ponsegromab or placebo§						
Any adverse event — no. (%)	4 (9)	2 (4)	5 (11)	4 (8)	11 (8)	15 (8)
Total no. of adverse events¶	7	4	8	5	17	24
Grades 1–2	7	3	6	5	14	21
Grade 3	0	1	2	0	3	3
Serious adverse event						
Patients with event — no. (%)	0	1 (2)	1 (2)	0	2 (1)	2 (1)
No. of serious events	0	1	1	0	2	2

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Patients with adverse event leading to discontinuation of ponsegromab or placebo — no. (%)	0	0	1 (2)	0	1 (1)	1 (1)
Adverse event occurring in ≥2 patients — no. (%)						
Malaise	0	1 (2)	1 (2)	0	2 (1)	2 (1)
Hypokalemia	1 (2)	0	0	1 (2)	1 (1)	2 (1)
Increase in aspartate aminotransferase	1 (2)	0	1 (2)	0	1 (1)	2 (1)

* All listed adverse events were reported after the first dose of ponsegromab or placebo and include all events that occurred either during the 12-week double-blind treatment period or during the subsequent follow-up until the first dose of open-label ponsegromab as part of the optional Part B extension period.
† One patient who was assigned to the placebo group completed the Part A period and entered Part B but did not receive any trial drug in Part B because of an adverse event. Thus, this death is not summarized in the Part A disposition (Fig. S5) but is listed in this table with Part A safety data.
‡ Among the patients who received ponsegromab, the deaths of 2 patients in the 100-mg group, 1 patient in the 200-mg group, and 3 patients in the 400-mg group that occurred during follow-up are not summarized in Figure S5.
§ The determination that an adverse event was related to ponsegromab or placebo was made by the investigator.
¶ No patient in any group had a grade 4 or fatal event that was determined to be related to ponsegromab or placebo.

GDF-15 levels are reported in several diseases — including heart failure,[29] chronic kidney disease,[30] and chronic obstructive pulmonary disease[31] — and are consistently associated with adverse outcomes.[29,30] Our finding of definitive disease modification associated with GDF-15 inhibition highlights the broad therapeutic potential for this mechanism of action, with possible implications for diseases beyond cancer cachexia. Ponsegromab is currently being evaluated in patients with heart failure and an elevated circulating GDF-15 level in a phase 2 trial.[32]

Although the minimum change in body weight that is considered to be clinically important has not been clearly established in patients with cancer cachexia, a weight gain of more than 5% has recently been suggested by the Cancer Cachexia Endpoints Working Group.[33] In our trial, patients in the 400-mg ponsegromab group exceeded 5% weight gain by 12 weeks in comparison with placebo. Weight gain alone is not considered to be a sufficient treatment goal for the multidimensional cachexia phenotype.[11] Here, we report improvements across weight and body composition, quality of life, and physical function driven by a single pharmacologic intervention directed against GDF-15. The observed ponsegromab-mediated improvements in appetite and reductions in cachexia symptoms, as assessed by FAACT-ACS and FAACT-5IASS, are considered to be moderate-sized improvements on the basis of standardized effect sizes.[34] The boosting of appetite in cancer cachexia improves quality of life and reduces emotional stress among patients.[35] Furthermore, the ponsegromab-mediated increase in nonsedentary physical activity may represent clinically meaningful functional improvement by enabling patients to complete important daily activities, such as showering, dressing, and light household activities.[36] Mechanistically, GDF-15 neutralization has been shown to restore muscle function and physical performance in a mouse model of cancer cachexia.[14] It is hypothesized that ponsegromab-mediated improvements in appetite and food intake may increase energy and the motivation to engage in activity, with attenuation of skeletal muscle loss through GDF-15 suppression also playing a role.

Ponsegromab was associated with weight gain in patients with even the most severe weight loss. The BMI-adjusted system of grading weight loss categorizes patients into grades 0 to 4, with

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grade 4 indicating more refractory cachexia and shortest survival.[37] Half the patients (50%) in this trial had a BMI-adjusted weight loss of grade 4; nevertheless, these patients had robust weight gain as compared with placebo in response to ponsegromab (Fig. 2). These results challenge the concept of refractory cachexia[2] and suggest that even patients with advanced cachexia may benefit from ponsegromab. Additional studies are needed to determine the appropriate timing for ponsegromab initiation along the cancer cachexia continuum.

In this population with advanced cancer, overall rates of adverse events were similar across groups and occurred in patients who were receiving a high rate (90%) of concurrent systemic anticancer therapies. Nausea and vomiting were reported less frequently in the ponsegromab group than in the placebo group (4% vs. 16% for nausea and 5% vs. 13% for vomiting). This observation is consistent with preclinical findings of GDF-15 inhibition[21] and with the appetite improvement that was observed in the trial. Furthermore, nausea and vomiting were the most frequently reported, dose-related adverse events in a phase 2 study of a GDF-15 agonist in patients with obesity, with nausea occurring in 71% and vomiting in 39% of patients.[38] In our trial, the early discontinuation rate (27%) and percentage of deaths (12%) before 12 weeks reflect rates that have been reported in previous clinical trials involving patients with cancer cachexia.[7,9] The placebo-like safety profile may differentiate ponsegromab from other agents used in cancer cachexia.[3]

Strengths of this trial include its broad inclusion criteria. We note a lack of racial diversity and adjustments for multiplicity as limitations. Although ponsegromab-mediated weight gain did not appear to be related to the magnitude of baseline GDF-15 elevation, larger studies are needed to evaluate conclusively whether the efficacy of ponsegromab could be proportional to GDF-15 elevation. In addition, data regarding activity level and gait that were collected by digital devices were not available for all the patients who completed week 12, a factor that may have limited detection of a treatment effect across all ponsegromab dose levels, together with the relatively short 12-week trial duration. Nonetheless, the improvement in physical activity that was observed in the 400-mg ponsegromab group is encouraging despite missing data. In addition, an imbalance in the percentage of patients who reported having a reduced appetite at baseline may have limited the opportunity to improve appetite-related symptoms in some groups. The definitions for having a response on FAACT subscales may require additional validation for regulatory purposes by means of alternative methods.[39]

Ponsegromab-mediated inhibition of GDF-15 resulted in a reduction in cachexia symptoms and increases in body weight, appetite, overall activity, and skeletal muscle mass as compared with placebo in patients with cancer cachexia and an elevated circulating GDF-15 level. These findings support the hypothesis that GDF-15 is a primary driver of cachexia and establish this cytokine as a potential therapeutic target for further evaluation in clinical trials.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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