SUPPLEMENTARY MATERIALS

A multicenter, open-label, single-arm study of anamorelin (ONO-7643) in patients with cancer cachexia and low body mass index

T. Naito, J. Uchino, T. Kojima, Y. Matano, K. Minato, K. Tanaka, T. Mizukami, S. Atagi, T. Higashiguchi, K. Muro, K. Takayama, J. Furuse, E. Morishima, T. Takiguchi, K. Tamura

Disclosures

Supplementary Methods

Key exclusion criteria, Prohibited therapies, Endpoints, Statistical analyses

Table S1. Percentage of patients with a composite clinical response (increase in body weight of ≥5% from baseline, an increase in FAQT-5IASS score of ≥2, and survival) at each time-point according to cancer type

Figure S1. Changes in body weight over time in the overall population (A), patients with NSCLC (B), and patients with GI cancers (C)

Figure S2. Changes in QOL-ACD item 8 (“Did you have a good appetite?”) scores over time in the overall population (A), patients with NSCLC (B), and patients with GI cancers (C)

Figure S3. Changes in QOL-ACD item 9 (“Did you enjoy your meals?”) scores over time in the overall population (A), patients with NSCLC (B), and patients with GI cancers (C)

Figure S4. Changes in QOL-ACD item 11 (“Did you lose any weight?”) scores over time in the overall population (A), patients with NSCLC (B), and patients with GI cancers (C)

Figure S5. Patient global impression of changes in appetite/eating-related symptoms (A, C, E) and overall condition (B, D, F) at 6 and 9 weeks in the overall population (A, B), patients with NSCLC (C, D), and patients with GI cancers (E, F)
DISCLOSURES

Tateaki Naito reports lecture fees and travel expenses from Ono Pharmaceutical, and institutional research funds from Ono Pharmaceutical in relation to this work; and institutional research funds from Otsuka Pharmaceutical outside the submitted work.

Junji Uchino, Yutaka Matano, Toru Kojima, and Koichi Minato report institutional research funds from Ono Pharmaceutical in relation to this work.

Kentaro Tanaka reports institutional research funds from Ono Pharmaceutical in relation to this work; and honoraria from AstraZeneca and Chugai outside the submitted work.

Takuro Mizukami reports institutional research funds from Ono Pharmaceutical in relation to this work; institutional research funds from Taiho Pharmaceutical and Eli Lilly outside the submitted work; and honoraria from Taiho Pharmaceutical, Chugai, Bayer, Merck Serono, Takeda, Eli Lilly, Asahi Kasei, Otsuka Pharmaceutical, Bristol-Myers Squibb, and Ono Pharmaceutical outside the submitted work.

Shinji Atagi reports institutional research funds from Ono Pharmaceutical in relation to this work; research grants from AstraZeneca, Eli Lilly, Ono Pharmaceutical, Taiho Pharmaceutical, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, MSD, Chugai, Merck, and F. Hoffmann-La Roche outside the submitted work; honoraria from AstraZeneca, Eli Lilly, Ono Pharmaceutical, Taiho Pharmaceutical, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, Hisamitsu, MSD, Chugai, Kyowa Hakko Kirin, Merck, Novartis Pharma, and Thermo Fisher Scientific outside the submitted work; and other financial or non-financial interests from F. Hoffmann-La Roche outside the submitted work.
Takashi Higashiguchi reports consultancy fees and travel expenses from Ono Pharmaceutical outside the submitted work.

Kei Muro reports consultancy fees, lecture fees, and travel expenses from Ono Pharmaceutical in relation to this work; institutional research funds from Solasia pharma, Merck Serono, Daiichi Sankyo, Parexel International, Pfizer, MSD, Amgen, Sanofi, and Taiho Pharma outside the submitted work; consultancy fees from Amgen, Ono Pharmaceutical, and AstraZeneca outside the submitted work; and honoraria from Ono Pharmaceutical, Sanofi, Taiho Pharma, Chugai, Takeda, Eli Lilly, BMS, and Bayer outside the submitted work.

Koichi Takayama reports consultancy fees, lecture fees, travel expenses, and institutional research funds from Ono Pharmaceutical in relation to this work; institutional research funds from Ono Pharmaceutical, Taiho Pharmaceutical, Eli Lilly, and Fukuda Lifetech outside the submitted work; lecture fees from Ono Pharmaceutical, Astrazeneca, MSD, Chugai-Roche, Eli Lilly, and Boehringer-Ingelheim outside the submitted work; and travel expenses from Ono Pharmaceutical outside the submitted work.

Junji Furuse reports consultancy fees, lecture fees, and travel expenses from Ono Pharmaceutical and institutional research funds from Ono Pharmaceutical in relation to this work; honoraria or personal fees from Ono Pharmaceutical, Bayer, Eisai, Eli Lilly Japan, MSD, Yakult Honsha, Chugai Pharma, Novartis Pharma, Astra Zeneca, Pfizer, Takeda, Taiho Pharmaceutical, Sannofy, Mylan EPD, EA Pharma, Kyowa Hakko Kirin, Daiichi Sankyo, Teijin pharma, Servier Japan, Incyte Japan outside the submitted work; and institutional research funds from Ono Pharmaceutical, MSD, Merck Bio, J-Pharma, Taiho Pharmaceutical, Takeda, Chugai Pharma, Astra Zeneca, Yakult Honsha, Eisai, Daiichi Sankyo, Mochida, Sanofi, Sumitomo Dainippon Bayer, Astellas, Incyte Japan outside the submitted work.
Eiichiro Morishima and Toru Takiguchi are employees of Ono Pharmaceutical.

Kazuo Tamura reports consultancy fees, lecture fees, travel expenses from Ono Pharmaceutical in relation to this work; consultancy fees from AC Medial outside the submitted work; and participation on advisory boards for Symbio and Eisai outside the submitted work.
SUPPLEMENTARY METHODS

Key exclusion criteria
Patients were excluded if they had an inability to orally ingest, digest, or absorb food and oral drugs; uncontrolled mental conditions; ascites, pleural effusions, or pericardial effusions requiring drainage or thoracentesis; uncontrolled edema; diminished cardiac function; or uncontrolled diabetes mellitus.

Prohibited therapies
Patients were prohibited from using any drugs or treatments for anorexia, such as systemic corticosteroids, growth hormone and androgen preparations, medroxyprogesterone and megestrol, Kampo medicines, and tube feeding. Adjuvant use of corticosteroid was allowed for up to 5 consecutive days in chemotherapy or radiotherapy regimens. Patients were also prohibited from using other drugs likely to interfere with the safety or efficacy of anamorelin.

Endpoints
Because of the possibility of missing measurements due to death, it was conditional that the patient was alive at each assessment point. Based on the prognosis of the cachectic cancer patients with BMI of <20 kg/m² obtained in previous clinical studies,1 9 weeks was selected for the primary endpoint evaluation to avoid a marked decrease in the number of evaluable patients due to missing data attributable to death.

Secondary endpoints were the changes in body weight and FAACT-5IASS score at 9 weeks.
Exploratory endpoints included the QOL questionnaire for cancer patients treated with anticancer drugs (QOL-ACD),2 and the patient’s global impression of change (PGIC).3-7

FAACT (version 4)8,9 and QOL-ACD were completed by the patients every 3 weeks during the
treatment. For QOL-ACD, we evaluated the changes for items 8, 9, and 11, covering appetite-related questions: “Did you have a good appetite,” “Did you enjoy your meals,” and “Did you lose any weight.” These items are scored on a 5-point scale, where 1 represents the worst perception and 5 represents the best perception. PGICs have been used to evaluate the patient’s perception of changes in disease/symptom severity over time, including cancer-related symptoms. In this study, the patients were asked, at 6 and 9 weeks, to rate whether their appetite/symptoms related to eating improved after starting treatment and how their general condition changed. Both questions comprised seven possible responses: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.

Each visit/assessment was performed on the scheduled day with a possible range of ±7 days.

**Statistical analyses**

The analysis using the multiple imputation method involved two steps:

1. A monotone missing data pattern was created for body weight and FAACT-5IASS score using the Monte-Carlo Markov Chain method.

2. The remaining missing data were imputed using a linear regression imputation model.

Predictors used in the multiple imputation method were baseline value, actual value at each assessment time, sex, age, number of anticancer treatment regimens (≤1, 2, ≥3), anticancer drug type (immunotherapy, other than immunotherapy), FAACT-5IASS score at baseline (≤10, >10), survival status on Day 169, duration to discontinuation of treatment, and carcinoma. No explicit imputation of survival status and postmortem data was conducted. When imputing missing data for the FAACT-5IASS score, the FAACT-5IASS score at baseline (≤10, >10) was excluded from the predictors. One hundred sets of complete data were created by imputing missing data.
References

1. Temel JS, Abernethy AP, Currow DC, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol*. 2016;17:519-531. doi:10.1016/s1470-2045(15)00558-6

2. Kurihara M, Shimizu H, Tsuboi K, et al. Development of quality of life questionnaire in Japan: quality of life assessment of cancer patients receiving chemotherapy. *Psychooncology*. 1999;8:355-363. doi:10.1002/(sici)1099-1611(199907/08)8:4<355::aid-pon401>3.0.co;2-i

3. Derry S, Wiffen PJ, Moore RA, et al. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. *Cochrane Database Syst Rev*. 2017;7:Cd012638. doi:10.1002/14651858.CD012638.pub2

4. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc*. 2002;77:371-383. doi:10.4065/77.4.371

5. Mercadante S, Adile C, Ferrera P, Casuccio A. Association between alcoholism and symptom expression, patient symptom goals, and clinical response in advanced cancer patients. *Support Care Cancer*. 2020;28:3361-3369. doi:10.1007/s00520-019-05152-x

6. Mercadante S, Adile C, Lanzetta G, et al. The lower the expectations in controlling the symptoms of advanced cancer patients, the better the clinical response. *Int J Clin Pract*. 2021;75:e13703. doi:10.1111/ijcp.13703

7. Moraska AR, Sood A, Dakhil SR, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: North Central Cancer Treatment Group NCCTG-N05C7 trial. *J Clin Oncol*. 2010;28:3673-3679. doi:10.1200/jco.2010.28.1444

8. Gelhorn HL, Gries KS, Speck RM, et al. Comprehensive validation of the functional assessment of anorexia/cachexia therapy (FAACT) anorexia/cachexia subscale (A/CS) in lung cancer patients with involuntary weight loss. *Qual Life Res*. 2019;28:1641-1653.
9. LeBlanc TW, Samsa GP, Wolf SP, Locke SC, Cella DF, Abernethy AP. Validation and real-world assessment of the Functional Assessment of Anorexia-Cachexia Therapy (FAACT) scale in patients with advanced non-small cell lung cancer and the cancer anorexia-cachexia syndrome (CACS). Support Care Cancer. 2015;23:2341-2347. doi:10.1007/s00520-015-2606-z
**Table S1.** Percentage of patients with a composite clinical response (increase in body weight of ≥5% from baseline, an increase in FAACT-5IASS score of ≥2, and survival) at each time-point according to cancer type

| Week | Overall population (N = 102) | NSCLC (N = 81) | GI cancer (N = 21) |
|------|-----------------------------|----------------|-------------------|
| 3    | 21 (20.6) [13.9–29.5]       | 16 (19.8) [12.6–29.8] | 5 (23.8) [10.6–45.1] |
| 6    | 34 (33.6) [25.1–43.2]       | 29 (36.1) [26.5–47.0] | 5 (23.8) [10.6–45.1] |
| 9    | 26 (25.9) [18.3–35.3]       | 23 (29.0) [20.1–39.7] | 3 (14.3) [5.0–34.6] |
| 12   | 29 (28.1) [20.2–37.8]       | 24 (29.3) [20.2–40.3] | 5 (23.8) [10.6–45.1] |
| 15   | 26 (25.5) [17.9, 35.0]      | 22 (27.2) [18.5–38.1] | 4 (19.0) [7.7, 40.0] |
| 18   | 26 (25.8) [18.3–35.2]       | 20 (25.1) [16.9–35.6] | 6 (28.6) [13.8, 50.0] |
| 21   | 26 (25.9) [18.3–35.3]       | 20 (25.2) [16.9–35.8] | 6 (28.7) [13.9–50.1] |
| 24   | 22 (21.9) [14.9–30.9]       | 16 (20.1) [12.7–30.2] | 6 (28.8) [13.9–50.2] |

Values are n (%) of patients [95% confidence interval]. Percentages were computed after applying the multiple imputation method for missing data at each time-point. The Wilson method\(^1\) was used to calculate 95% confidence intervals using complete data after imputing missing data.

Abbreviations: FAACT-5IASS, Functional Assessment of Anorexia/Cachexia Therapy 5-item Anorexia Symptom Scale; NSCLC, non-small cell lung cancer; GI, gastrointestinal.

**Reference**

1. Lott A, Reiter JP. Wilson confidence intervals for binomial proportions with multiple imputation for missing data. *Am Stat.* 2020;74:109-115. doi:10.1080/00031305.2018.1473796
Figure S1. Changes in body weight over time in the overall population (A), patients with NSCLC (B), and patients with GI cancers (C).

Values are mean ± standard deviation for patients with available data at each time-point.

Abbreviations: GI, gastrointestinal; NSCLC, non-small cell lung cancer.
Figure S2. Changes in QOL-ACD item 8 (“Did you have a good appetite?”) scores over time in the overall population (A), patients with NSCLC (B), and patients with GI cancers (C).

Values are mean ± standard deviation for patients with available data at each time-point.

Abbreviations: GI, gastrointestinal; NSCLC, non-small cell lung cancer; QOL-ACD, QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs.
Figure S3. Changes in QOL-ACD item 9 (“Did you enjoy your meals?”) scores over time in the overall population (A), patients with NSCLC (B), and patients with GI cancers (C).

Values are mean ± standard deviation for patients with available data at each time-point.

Abbreviations: GI, gastrointestinal; NSCLC, non-small cell lung cancer; QOL-ACD, QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs.
Figure S4. Changes in QOL-ACD item 11 (“Did you lose any weight?”) scores over time in the overall population (A), patients with NSCLC (B), and patients with GI cancers (C).

Values are mean ± standard deviation for patients with available data at each time-point.

Abbreviations: GI, gastrointestinal; NSCLC, non-small cell lung cancer; QOL-ACD, QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs.
**Figure S5.** Patient global impression of changes in appetite/eating-related symptoms (A, C, E) and overall condition (B, D, F) at 6 and 9 weeks in the overall population (A, B), patients with NSCLC (C, D), and patients with GI cancers (E, F).

Data were missing for 9 patients at 6 weeks and 15 at 9 weeks.
Data were missing for 8 patients at 6 weeks and 13 at 9 weeks.
Data were missing for 1 patient at 6 weeks and 2 at 9 weeks.

Values are percentages of patients.

Abbreviations: GI, gastrointestinal; NSCLC, non-small cell lung cancer.