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Original Article

Association between the Pretreatment Body Mass Index and Anamorelin's Efficacy in Patients with Cancer Cachexia: A Retrospective Cohort Study

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Anamorelin (ANAM) is used to treat cancer-associated cachexia, a syndrome involving muscle loss and anorexia. The timing of the initiation of ANAM treatment is crucial to its efficacy. Although the body mass index (BMI) is a diagnostic criterion for cancer cachexia, no studies have explored its association with ANAM efficacy. We conducted a single-center, retrospective cohort study to investigate the association between the pre-treatment BMI and ANAM efficacy in patients with cancer-associated cachexia (n = 47). The ANAM treatment was considered effective if the patient's appetite improved within 30 days of treatment initiation. We calculated a BMI cutoff value (19.5 kg/m^2) and used it to divide the patients into high- and low-BMI groups. Their background, clinical laboratory values, cancer types, and treatment lines were investigated. Twenty (42.6%) had a high BMI (≥ 19.5 kg/m^2) and 27 (57.4%) had a low BMI (< 19.5 kg/m^2). High BMI was significantly associated with ANAM effectiveness (odds ratio 7.86, 95% confidence interval 1.99-31.00, $p = 0.003$). Together these results indicate that it is beneficial to initiate ANAM treatment before a patient's BMI drops below 19.5 kg/m^2. Our findings will help advance cancer cachexia treatment and serve as a reference for clinicians to predict ANAM's efficacy.

Key words: anamorelin, cancer-associated cachexia, body mass index, albumin, efficacy rate

Cachexia is a condition associated with anorexia, inflammation, and muscle wasting that occurs in 50-80% of individuals with advanced cancer, thus representing a substantial health concern in these patients [1]. Cancer cachexia is classified into three stages: pre-cachexia, cachexia, and refractory cachexia. The pre-cachexia and cachexia stages are considered reversible with combination therapy, including nutritional support, exercise, and pharmacotherapy; the refractory cachexia stage is deemed irreversible. Numerous factors influence the severity of cancer cachexia, including weight loss, skeletal muscle mass, Eastern Cooperative Oncology Group performance status (ECOG-PS), and body mass index (BMI) [2], with the risk of cachexia increasing as the BMI decreases [3, 4]. Cachexia not only presents typical symptoms — *e.g.*, weight loss, muscle mass loss, and loss of appetite — but also diminishes the efficacy of chemotherapy [5] and affects survival rates [6]. The treatment options for anorexia and weight loss are limited, despite the emphasized need for preventive management [7].

Anamorelin (ANAM) was approved for use in Japan in January 2021. ANAM is a novel pharmacological treatment for cancer cachexia that mimics the action of ghrelin, a peptide hormone produced by endocrine cells

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in the stomach that stimulates hunger. ANAM binds to the ghrelin receptor (GHS-R1a), stimulates the release of growth hormone (GH) from the pituitary gland, and activates the hypothalamus, thereby increasing one's appetite [8]. Growth hormone released from the pituitary gland promotes muscle protein synthesis through the secretion of insulin-like growth factor 1 (IGF-1) from the liver [9]. These mechanisms suggest that ANAM exerts its effects on weight gain by stimulating the secretion of GH via the activation of GHS-R1a and enhancing appetite [10].

A Japanese study of gastrointestinal cancers (colorectal, gastric, and pancreatic cancer; ONO-7643-05) demonstrated the beneficial effects of ANAM on body weight and anorexia [10]. In a post-hoc subgroup analysis of that study, the benefits and safety of ANAM compared with a placebo were assessed in various subgroups, showing benefits for weight and anorexia in almost all subgroups [11]. However, our search of the relevant literature identified no reports of an investigation of the association between differences in patient background and the effectiveness of ANAM as a primary outcome. The patient population for whom ANAM is most beneficial has thus been unclear.

Given the close relationship between cancer cachexia and BMI [4, 12-14], we speculated that the BMI may influence aspects of ANAM's efficacy. Clarifying this relationship will contribute to the appropriate use of ANAM in the treatment of cancer cachexia. We conducted the present study to analyze the association between the pretreatment BMI and the efficacy of ANAM in patients with cancer cachexia treated at Fukuyama Medical Center (Hiroshima, Japan).

Materials and Methods

Study design and participants. To investigate the association between the pretreatment BMI and the efficacy of ANAM in patients with cancer cachexia introduced to ANAM, this single-center retrospective cohort study analyzed the data of 55 patients treated with ANAM for cancer cachexia during hospitalization or outpatient visits at the Fukuyama Medical Center (hereafter referred to as "our hospital") between June 1, 2021 and November 30, 2023.

The enrollment protocol is shown in Fig. 1. The data of the patients at the time of the introduction of ANAM were included in the analyses; the data of those for whom the drug was restarted after a temporary interruption due to side effects were excluded. Patients who discontinued treatment immediately after ANAM initiation due to side effects such as nausea and patients who self-interrupted treatment after ANAM initiation were also excluded due to the difficulty in evaluating the drug efficacy. ANAM was administered to patients with a weight loss ≥ 5% within 6 months, anorexia, and two or more of the following: (1) fatigue or malaise, (2) generalized muscle weakness, (3) one or more of the

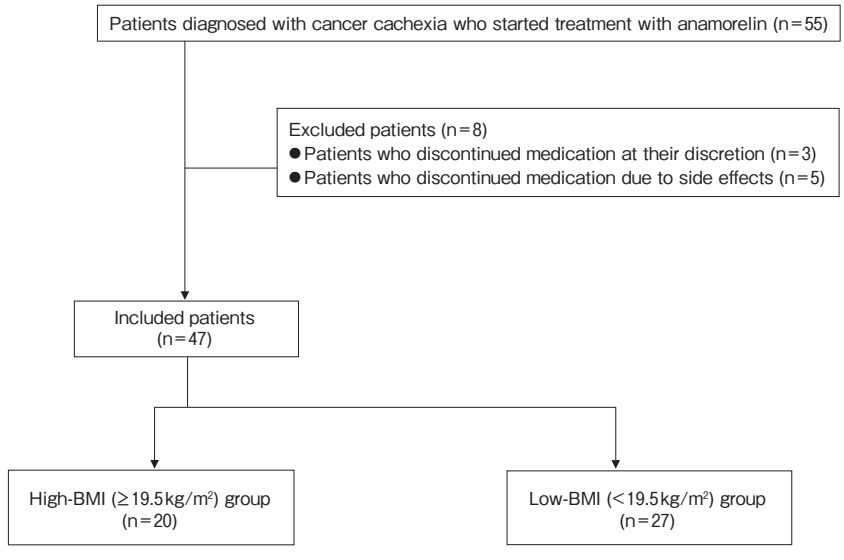

Fig. 1 Flowchart of patient selection. BMI, body mass index.

following: C-reactive protein (CRP) level ≥ 0.5 mg/dL, hemoglobin (Hb) level < 12 g/dL, and albumin (Alb) level < 3.2 g/dL.

Fatigue, malaise, and generalized muscle weakness were assessed according to the Common Terminology Criteria for Adverse Events ver. 5.0, with grade ≥ 1 defined as symptoms. The cancer types in this study were limited to non-small cell lung, gastric, pancreatic, and colorectal cancers, as described in the Japanese package insert.

Data collection. We used the patients' medical records to gather the following information: age, sex, ECOG-PS, range and percentage of body weight loss within the past 6 months from the date of ANAM initiation, body weight and BMI at ANAM initiation; weight change during the first 12 weeks of ANAM administration; the number of days from diagnosis of unresectable or advanced recurrent cancer to the initiation of ANAM, the severity of cancer cachexia; the concomitant use of drugs associated with increased or decreased appetite (*e.g.*, steroids, mirtazapine), CYP3A inhibitors involved in ANAM pharmacokinetics, and CYP3A inducers; the cancer type, stage, treatment line(s), and concomitant cancer therapy; laboratory values before treatment initiation; and days between ANAM initiation and death (survival duration).

Clinical endpoints and definitions. The efficacy of ANAM was compared between the high- and low-BMI groups, and the optimal BMI cutoff value was calculated using efficacy as the objective variable. We compared the number of days to the invalidity of ANAM between the high- and low- BMI groups and between the patients with cachexia and those with refractory cachexia by using the reported classification [2]. We also compared the ANAM efficacy rates with survival durations (≤ 60 days, 61-120 days, and > 120 days). In the cases in which treatment was deemed effective, the changes in body weight measured over 12 weeks were also evaluated.

Efficacy was defined as an improvement in appetite within 30 days of the start of ANAM treatment in patients who continued ANAM treatment. The presence or absence of increased appetite was determined based on the patient's subjective evaluation during the treating physician's interview. Outpatients undergoing anticancer drug treatment attended the clinic every 2, 3, or 4 weeks based on the schedule of their anticancer drug treatment, and it was difficult to uniformly determine the evaluation date. We thus defined the efficacy evaluation date as within 30 days in this study. Refractory cachexia was defined as an ECOG-PS of ≥ 3 and death within 3 months of ANAM initiation.

Statistical analyses. The Mann–Whitney *U*-test was used for group comparisons of continuous variables; Fisher's exact probability test was used to test categorical variables, and the Cochran–Armitage test was used to assess the trends among levels of ordinal variables, with a significance level of < 0.05; both sides were observed to be significant. For the BMI data, receiver operating characteristic (ROC) curves were used to calculate the cutoff values for predicting the ANAM treatment's effectiveness. We performed univariate and multiple logistic regression analyses with improvement in appetite with ANAM treatment as the objective variable in order to examine the factors affecting the efficacy of ANAM. Lastly, the Kaplan–Meier method and log-rank test were used to calculate the number of invalid days. All statistical analyses were performed using EZR software (ver. 1.54) (Jichi Medical University Saitama Medical Center).

Ethical concerns. This study was conducted in compliance with Japan's Ethical Guidelines for Medical Research Involving Human Subjects and the Appropriate Handling of Personal Information by Medical and Nursing Care Providers guidelines and was approved by the Ethics Review Committee of Fukuyama Medical Center (approval no. ERBP2023041).

Results

ROC curve analysis of the BMI and ANAM's efficacy. The optimal BMI cutoff value (19.5 kg/m^2) was calculated with efficacy as the objective variable (area under the ROC curve, 0.739; sensitivity, 0.682; specificity, 0.800). We used this cutoff value to compare patient groups' clinical outcomes.

Comparison of clinical characteristics and efficacy rates between the high- and low-BMI groups. The baseline patient characteristics are shown in Table 1. Forty-seven patients were included in this study. The baseline weight was significantly higher in the high-BMI group. Age, sex, ECOG-PS, the body weight loss range and rate, and concomitant drug use (including CYP3A4 inhibitors/inducers, mirtazapine, and others) did not differ significantly between the high- and low-BMI groups. Among the patients undergoing chemo-

Table 1 Patient characteristics

Characteristic	Overall (n=47)	High-BMI group (n=20)	Low-BMI group (n=27)	*P*-value
Age, years	73 (66, 78)	73 (69, 78)	73 (66, 78)	0.682
Female, n (%)	19 (40.4%)	10 (50.0%)	9 (33.3%)	0.368
ECOG-PS (0-1), n (%)	18 (38.3%)	10 (50.0%)	8 (29.6%)	0.226
Baseline body weight, kg	48 (43.9, 52.6)	51.8 (46.7, 54.5)	45.8 (42.1, 50.2)	**0.008**
Weight loss within six months prior to treatment, kg	6.4 (4.4, 10.0)	6.4 (5.5, 10.3)	6.4 (4.1, 9.0)	0.505
Weight loss rate within six months prior to treatment (%)	11.7 (8.6, 16.3)	11.2 (9.6, 16.2)	12.1 (7.9, 16.5)	0.940
Concomitant steroid use, n (%)	10 (21.3%)	3 (15.0%)	7 (25.9%)	0.481
Days from diagnosis of unresectable advanced recurrent cancer to ANAM induction, days	268 (93, 451)	261 (96, 370)	259 (82, 534)	0.788
Severity of cancer cachexia, n (%)				
Cachexia	36 (76.6%)	16 (80.0%)	20 (74.1%)	0.737
Refractory cachexia	11 (23.4%)	4 (20.0%)	7 (25.9%)	
Cancer type, n (%)				
Pancreatic cancer	15 (31.9%)	6 (30.0%)	9 (33.3%)	0.444
Gastric cancer	15 (31.9%)	5 (25.0%)	10 (37.0%)	
Colorectal cancer	11 (23.4%)	7 (35.0%)	4 (14.8%)	
Non-small cell lung cancer	6 (12.8%)	2 (10.0%)	4 (14.8%)	
Cancer stage, n (%)				
Stage III	5 (10.6%)	2 (10.0%)	3 (11.1%)	1.000
Stage IV	24 (51.1%)	10 (50.0%)	14 (51.9%)	
Recurrence of cancer	18 (38.3%)	8 (40.0%)	10 (37.0%)	
Treatment line, n (%)				
First line	16 (34.0%)	7 (35.0%)	9 (33.3%)	1.000
Second line	8 (17.0%)	6 (30.0%)	2 (7.4%)	0.057
Third line and above	10 (21.3%)	1 (5.0%)	9 (33.3%)	**0.029**
Concomitant cancer therapy, n (%)				
Chemotherapy ± Molecular targeted Therapy	25 (34.1%)	12 (60.0%)	13 (48.1%)	0.556
Chemotherapy + ICI	5 (22.0%)	1 (5.0%)	4 (14.8%)	0.377
ICI	2 (9.8%)	0 (0.0%)	2 (7.4%)	0.500
Tyrosine kinase inhibitor	1 (4.9%)	0 (0.0%)	1 (3.7%)	1.000
Radiation therapy	1 (2.1%)	1 (5.0%)	0 (0.0%)	0.426
Best supportive care	13 (27.7%)	6 (30.0%)	7 (25.9%)	1.000
Laboratory data				
CRP, mg/dL	0.84 (0.35, 2.49)	0.99 (0.48, 2.72)	0.69 (0.30, 2.34)	0.445
Hemoglobin, g/dL	10.2 (9.3, 11.8)	10.8 (9.4, 12.1)	10.2 (9.3, 11.3)	0.498
Albumin, g/dL	3.1 (2.7, 3.6)	3.1 (2.5, 3.5)	3.2 (2.9, 3.6)	0.597
AST, U/L	23.0 (17.5, 34.5)	24.5 (16.0, 33.3)	23.0 (18.0, 35.5)	0.897
ALT, U/L	17.0 (8.0, 25.0)	17.0 (8.8, 27.8)	16.0 (8.0, 24.5)	0.605
ALP, U/L	97.0 (75.5, 130.0)	109.5 (86.8, 136.8)	95.0 (71.0, 118,0)	0.355
γ-GTP, U/L	43.0 (23.0, 80.0)	41.5 (18.3, 97.3)	43.0 (28.0, 80.0)	0.988
Total bilirubin, mg/dL	0.6 (0.4, 1.0)	0.6 (0.6, 1.0)	0.6 (0.4, 1.1)	0.763

Data are presented as medians (interquartile range, 25-75th percentile) or numbers (percentages). *$P<0.05$ was considered statistically significant.

BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group performance status scale; ICI, immune checkpoint inhibitor; CRP, C-reactive protein; AST, aspartate aminotransaminase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase.

therapy, there were significantly more patients in the low-BMI group who were on a 3rd-line or further-line treatment ($p=0.026$). There were no significant between-group differences in cancer type, stage, or laboratory data before treatment initiation. The ANAM efficacy rate was significantly higher in the high-BMI group compared to the low-BMI group (80.0% vs. 32.3%, $p=0.001$).

Factors related to ANAM efficacy determined by the multiple logistic regression analysis. Factors related to the efficacy of the ANAM treatment in the patients with cancer cachexia were analyzed by both univariate and multiple logistic regression analyses (Table 2). In the univariate analysis, the significant variables were BMI ≥ 19.5 kg/m^2 and ECOG-PS at 0-1 (vs. 2-3). In the multivariate analysis, considering the factors identified in a previous study [15], ECOG-PS 0-1 (vs. 2-3) was adjusted for model 1, with efficacy as the dependent variable. Only BMI ≥ 19.5 kg/m^2 emerged as a significant factor (odds ratio [OR] 7.86; 95% confidence interval [CI]: 1.99-31.00; $p=0.003$).

Model 2, with efficacy as the dependent variable, was adjusted for Alb level ≥ 3.2 g/dL [2], which is the diagnostic criterion for cancer cachexia. BMI ≥ 19.5 kg/m^2 (OR 15.70, 95%CI: 2.92-84.80, $p=0.001$) and an Alb level ≥ 3.2 g/dL (OR 6.05, 95%CI: 1.14-32.00, $p=0.034$) emerged as significant factors.

Comparison of the efficacy rate and survival duration after ANAM initiation. All patients in the study were evaluated for efficacy within 30 days of the initiation of ANAM treatment, and the analyses revealed an overall ANAM efficacy rate of 46.8%. A trend toward higher efficacy rates was observed with longer survival durations after the initiation of ANAM (Cochran–Armitage test, $p=0.004$, Fig. 2).

Comparison of ANAM's efficacy by the severity of cancer cachexia. The number of days until the ANAM treatment became ineffective within 30 days was compared between the high- and low-BMI groups (Fig. 3). The time until the ANAM became ineffective was significantly shorter in the low-BMI group than in the high-BMI group ($p=0.003$).

We divided the patients into cachexia and refractory cachexia groups, and the number of days to invalida-

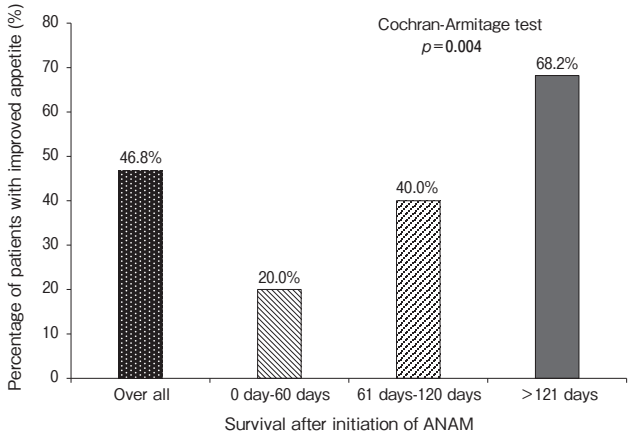

Fig. 2 The overall efficacy and the association between survival duration and efficacy after the initiation of anamorelin (ANAM) treatment. We categorized the patients into three groups based on their survival duration: those with a survival duration within 60 days from the start of ANAM treatment to death, 61-120 days, and >120 days; the efficacy rate for each group is indicated.

Table 2 Logistic regression analysis of factors associated with the efficacy of anamorelin

	Univariate model			Multivariate model 1			Multivariate model 2		
	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
Age, per 1-year increase	1.03	0.96–1.11	0.428						
Sex; female	1.04	0.32–3.34	0.949						
BMI, ≥19.5 kg/m^2	8.57	2.27–32.40	**0.002**	7.86	1.99–31.00	**0.003**	15.70	2.92–84.80	**0.001**
Range of weight loss, 1 kg decrease	1.02	0.87–1.19	0.828						
Percentage of weight loss, 1% decrease	0.98	0.87–1.10	0.681						
ECOG-PS, 0–1 (vs. 2–3)	3.80	1.10–13.20	**0.035**	3.28	0.81–13.20	0.096			
Alb, ≥3.2 g/dL	2.57	0.79–8.35	0.117				6.05	1.14–32.00	**0.034**

P<0.05 was considered statistically significant.
BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group performance status scale; Alb, albumin; OR, odds ratio; CI, confidence interval.

tion within 30 days was compared (Fig. 4): a significantly shorter time to invalidation was observed in the refractory cachexia group compared to the cachexia group ($p < 0.001$).

Weight fluctuations in the patients for whom ANAM was effective. Among the 22 patients with effective ANAM treatment, 18 weighed themselves within 12 weeks of treatment (Fig. 5), and there were no significant differences between the groups.

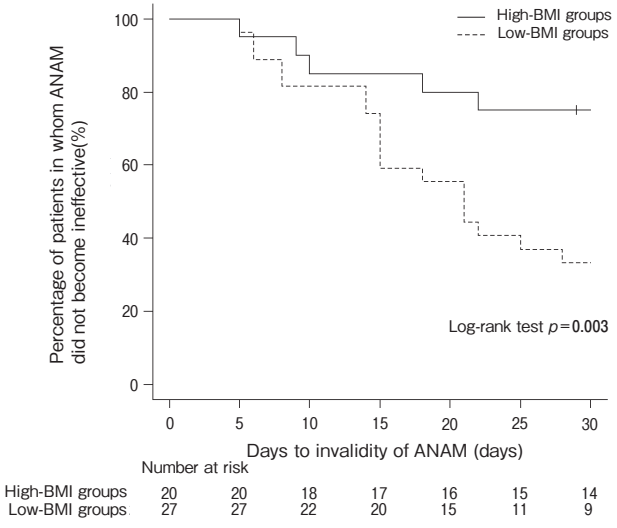

Fig. 3 The length of time from the start of ANAM treatment to the determination of invalidity in the high-and low-BMI groups.

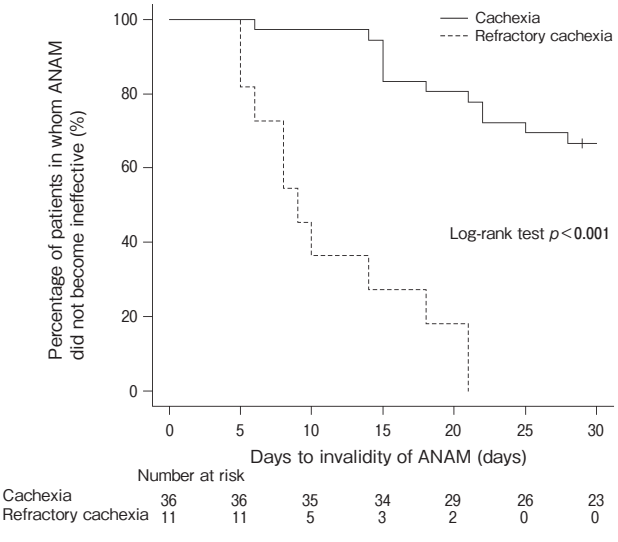

Fig. 4 The length of time from the start of ANAM treatment to the determination of invalidity of cachexia and refractory cachexia.

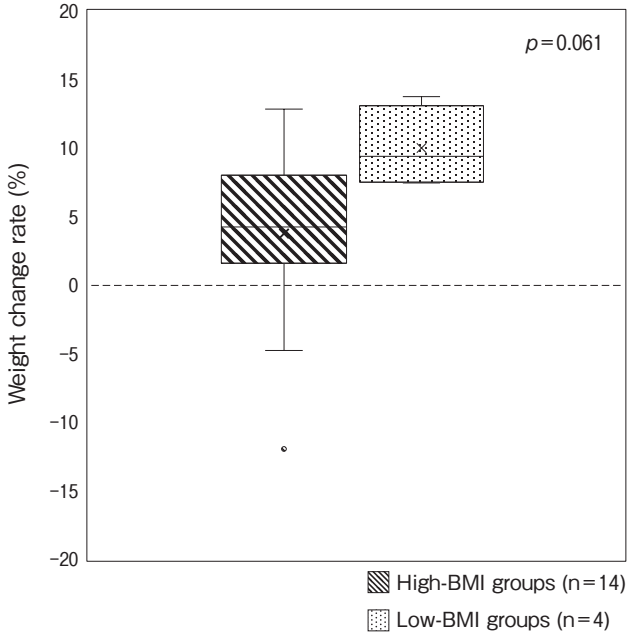

Fig. 5 Box plots comparing the percentage change in the patients' body weight after they started ANAM treatment. In each box, the *central mark* represents the median, the *cross mark* indicates the average, and the *edges* correspond to the 25th and 75th percentiles. The *upper and lower whiskers* represent the maximum and minimum values, respectively. The Mann–Whitney *U*-test was used for the analyses. $p = 0.061$.

Discussion

The findings of this study suggest that among patients with cancer cachexia, the pretreatment BMI influences the efficacy of ANAM treatment. Specifically, the initiation of ANAM treatment before a patient's BMI falls to < 19.5 kg/m^2 was shown to be beneficial. To our knowledge, this is the first study to demonstrate a relationship between ANAM treatment's efficacy and patients' BMI in a real-world clinical setting.

This study's findings align with those of earlier research, demonstrating appetite improvement in a subset of patients following ANAM treatment [10, 16-18]. However, in the present investigation, the appetite-enhancing effects of ANAM were limited in the low-BMI group. There are two main reasons for this result. First, a low BMI may be a consequence of the progression of cachexia. An association between cachexia progression and lower BMI has been reported [3, 4], and the BMI is one of the diagnostic criteria for cachexia [2]. Several research groups have suggested

that this is because the inhibition of ghrelin suppresses an individual's appetite due to an increase in inflammatory cytokines as cachexia progresses [19-21]. Although we did not examine the levels of cytokines such as interleukin (IL)-1α, IL-1β, and IL-6 and tumor necrosis factor (TNF)-α released from cancer and tumor-bearing hosts in this study, it is possible that an excessive inflammatory cytokine production associated with cachexia progression was induced and limited the efficacy of ANAM in the low-BMI group. Our additional analyses that divided the patients into cachexia and refractory cachexia groups showed that the degree of the progression of cancer cachexia may interfere with the benefit of ANAM treatment (Fig. 4), thus supporting the need for early intervention in the pre-cachexia stage [22, 23].

Second, a low BMI may have reflected an early deterioration in the patient's general health and nutritional status. Dewys *et al.* described an association between weight loss in patients with cancer and a decrease in the ECOG-PS [24]. These processes are not simultaneous; the decrease in BMI precedes the decrease in ECOG-PS [2, 16]. The European Palliative Care Research Collaborative classification of cancer cachexia stages does not include PS criteria for the pre-cachexia or cachexia stages, but a decline in PS is included in the diagnostic criteria for refractory cachexia [2]. In the present study, the BMI may thus have been identified as an indicator of effectiveness because a decrease in BMI was observed before a decrease in the PS.

Takayama *et al.* conducted post-hoc analyses of the ONO-7643-04 study and reported that in patients with an ECOG-PS of 2, ANAM treatment tended to suppress weight loss compared with a placebo, and the effect of weight gain with ANAM treatment was lesser compared to that in patients with an ECOG-PS of 0-1 [11]. Similar results that support our present findings concerned the effect of ANAM treatment on appetite improvement [11]. The association between the serum Alb level, which is a marker of nutritional status and inflammation, and the efficacy of ANAM has been described [15, 25]. Since Alb is also included in the diagnostic criteria for cancer cachexia [26], patients with low Alb levels may have progressive cancer cachexia, and this may limit the efficacy of ANAM. However, Alb values are affected by various factors, including malnutrition but also overhydration, dehydration, and capillary permeability [27].

In this study's univariate analysis, Alb did not show statistical significance, suggesting that it is likely influenced by other factors. In contrast, the BMI can be used as a more direct clinical indicator because it seems to be a more appropriate clinical measure. Our results suggest that the determination of whether a patient's BMI is above or below 19.5 kg/m^2 may be useful as an indicator for initiating ANAM treatment, in combination with reported factors such as the ECOG-PS and Alb.

Our evaluation of the weight changes in the patients who responded to ANAM treatment revealed that weight gain occurred in many of these patients, regardless of whether they had a high or low BMI. However, some patients lost weight despite gaining an improved appetite. Many of the major events that induce cachexia are likely mediated through the central nervous system and include metabolic abnormalities such as hypermetabolism and inflammation-related anorexia [28]. It is therefore difficult to stop a patient's weight loss by improving appetite alone, and multidisciplinary treatment (including not only pharmacotherapy but also exercise therapy) is needed. The present low-BMI group tended to have a higher rate of weight gain, but the small number of cases means that this interpretation should be made with caution. Since the weight progress of the non-response group could not be tracked, the results might have changed if the non-response group had been included in this analysis.

This study has several limitations. The sample size was limited, and this was a single-center retrospective observational study. Future investigations with larger sample sizes are required. Nonetheless, we considered data encompassing various cancer types, which is valuable for real-world clinical practice. Second, we did not include all possible causes of appetite loss. Factors such as a history of colorectal or pancreatic resection, ileus, psychological resistance to eating, and diminished digestive enzyme levels were not fully accounted for. We also did not examine changes in the patients' dietary intake, including specific calorie consumption. Obtaining such objective data daily in clinical practice is challenging unless the patient is hospitalized. Third, cancer-related cachexia is a multifactorial metabolic disorder requiring multifaceted treatment modalities including medication(s), nutritional supplementation, and exercise therapy. Because this was a retrospective study, the influence of dietary and exercise interven-

tions on the ANAM treatment's effectiveness was not considered. Fourth, weight fluctuations could not be confirmed in some of the patients who benefited from the ANAM treatment, and even in the cases with fluctuations, the timing of the observations varied. Moreover, weight gain can be due to fluid retention presenting as edema, and the inability to elucidate these possibilities is another study limitation. However, we believe that the efficacy of ANAM treatment usually begins with improved appetite, and many patients gained weight as a result of improved appetite. Fifth, although the results of this study indicate that the BMI is a predictor of the effectiveness of ANAM treatment, the effects of edema, dehydration, and other factors on weight were not initially evaluated.

In conclusion, our findings suggest that initiating ANAM treatment before a patient's BMI is < 19.5 kg/m^2 is beneficial, and an early initiation of ANAM treatment when indicated and before the progression of cancer cachexia may improve appetite. This study's findings could contribute to the advancement of medical care for cancer cachexia, and they serve as a crucial reference for clinicians and other healthcare professionals in predicting the efficacy of ANAM treatment in the management of patients with cancer cachexia.

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