

Impact of Cancer Cachexia on Treatment With PD-1/PD-L1 Inhibitors Plus Chemotherapy in Advanced Non-small-Cell Lung Cancer

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Research Article

Keywords: Non-small cell lung cancer, Cancer cachexia, Programmed cell death-1, Programmed death-ligand 1, PD-1/PD-L1 inhibitor plus chemotherapy

Posted Date: June 24th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-524527/v1>

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Abstract

Purpose

Programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors plus chemotherapy has become the standard first-line treatment in patients with advanced non-small-cell lung cancer (NSCLC). However, few studies have explicitly focused on the impact of cancer cachexia on the efficacy of PD-1/PD-L1 inhibitors plus chemotherapy. Thus, we evaluated the clinical implications of cancer cachexia on the survival outcomes in patients who received this treatment.

Methods

We conducted a retrospective review of medical records of patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors plus chemotherapy from December 2018 to December 2020. Cancer cachexia was diagnosed as an unintentional weight loss of 5% or more over six months. We evaluated the progression-free survival (PFS) and overall survival (OS) for patients with or without cancer cachexia who received PD-1/PD-L1 inhibitors plus chemotherapy.

Results

Among the 80 included patients, 37 (46%) had cancer cachexia. Cachectic patients had a lower objective response rate (30 vs 51%, $P < 0.05$), poorer PFS (2.3 vs 12.0 months, $P < 0.05$), and poorer OS (10.8 vs 23.9 months, $P < 0.05$) than non-cachectic patients. The Cox proportional-hazard ratios (95% confidence interval) of cancer cachexia were 1.77 (1.01–3.10) for PFS and 2.90 (1.40–6.00) for OS, with adjustments for Eastern Cooperative Oncology Group performance status, PD-L1 tumour proportion score, histology, and central nervous system metastases.

Conclusion

Pre-treatment cancer cachexia may reduce treatment efficacy and shorten survival time in patients receiving PD-1/PD-L1 inhibitors plus chemotherapy. Early evaluation and intervention for cancer cachexia might improve oncological outcomes in patients with advanced NSCLC.

1. Introduction

In recent years, programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors have led to significant advances in the treatment of patients with advanced non-small-cell lung cancer (NSCLC). [1–4] In the first-line treatment of patients with advanced NSCLC, the addition of pembrolizumab to platinum-based chemotherapy demonstrated improved progression-free survival (PFS) and overall survival (OS). [5, 6] Furthermore, in the IMpower150 study, the addition of atezolizumab to bevacizumab, carboplatin, and paclitaxel for the first-line treatment of patients with metastatic non-squamous NSCLC significantly improved PFS and OS. [7]

Cancer cachexia is a multiple-factor disorder characterized by weight loss. [8, 9] The adverse effect of cancer cachexia on the efficacy of PD-1 and PD-L1 inhibitors has been previously demonstrated in several studies. [10, 11] Additionally, our previous studies have shown that cancer cachexia is an independent adverse predictive factor for the effect of PD-1 or PD-L1 inhibitors on anti-tumour efficacy after adjusting for other clinical factors. Furthermore, cancer cachexia potentially has a desensitizing effect in patients with high PD-L1 expression who potentially have an increased sensitivity to PD-1 or PD-L1 inhibitors. [12]

PD-1/PD-L1 inhibitor plus chemotherapy might not be effective for all patients with advanced NSCLC. [5–7] Thus, it is essential to identify populations that do not respond to PD-1/PD-L1 plus chemotherapy to achieve further survival benefits. Accordingly, this study aimed to evaluate the clinical impact of cancer cachexia on a clinical outcome in patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors plus chemotherapy.

2. Methods

2.1. Patients

Between December 2018 and December 2020, 130 consecutive patients with advanced NSCLC were treated with PD-1/PD-L1 inhibitor plus chemotherapy in the Shizuoka Cancer Center. To evaluate patient eligibility, the patients' medical records were retrospectively reviewed. The exclusion criteria were as follows: (1) participation in clinical trials, (2) unknown weight change over six months before the start of PD-1/PD-L1 inhibitors plus chemotherapy, and (3) not evaluable for objective response to PD-1/PD-L1 inhibitors plus chemotherapy based on Response Evaluation Criteria for Solid Tumours (RECIST) version 1.1. [13]

2.2. Data collection

Body weight was measured in kilograms, and BMI (kg/m^2) was calculated. Immunohistochemical staining of the tumour biopsy specimens was performed using a monoclonal antibody against PD-L1 (22C3 pharm Dx assay, Agilent Technologies, Santa Clara, CA, USA). PD-L1 expression on tumour cells was categorised by the tumour proportion score (TPS), defined as the percentage of tumour cells presenting with PD-L1 staining. The disease stage was determined based on the 8th edition of the TNM classification of lung cancer. [14] Objective tumour responses were assessed according to RECIST version 1.1. [15] Any adverse events were evaluated using the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 5.0. The data cut-off date was December 31, 2020.

Cancer cachexia was diagnosed as unintentional weight loss of 5% or more in the six months prior to the start of PD-1/PD-L1 inhibitor plus chemotherapy. [9] Over the prior six months, the weight change of patients was obtained by interviewing the patients and their families. Skeletal muscle mass and BMI were not included in the definition of cancer cachexia.

2.3. Statistical analysis

The Chi-square or Fisher exact tests were used for comparison of all categorical variables. PFS and OS were defined from the start of the PD-1 / PD-L1 inhibitor plus chemotherapy, as estimated by the Kaplan-Meier method and compared using the log-rank test. The end of the follow-up period was set at December 31, 2020. Potential predictive factors for PFS and OS were assessed using a Cox proportional hazards model. For the univariate analyses, the covariates included cancer cachexia (cachexia vs. non-cachexia), age (≥ 75 vs. <75), sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG-PS) (0 vs. 1), histology (non-squamous vs. squamous), BMI (≥ 25 vs. <25 kg/m²), PD-L1 TPS ($\geq 50\%$ vs. $<50\%$ or unknown), and central nervous system (CNS) metastases. Factors with univariate *P*-values less than 0.05 or known prognostic factors such as PD-L1 TPS, histology, ECOG-PS, and CNS metastases were included in the multivariate analysis. For all analyses, *P*-values less than 0.05 were defined as significant. All analyses were conducted using STATA software (version 14.0; Stata Corp., College Station, TX).

3. Results

3.1. Patient characteristics

Eighty of 130 consecutive patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors plus chemotherapy as 1st-line therapy between December 2018 and October 2020 at our institution were finally included in our analysis. We excluded twenty-eight patients who participated in clinical trials, 21 patients with unknown weight changes, and one patient whose objective tumour response could not be evaluated (Fig. 1).

The median age was sixty-seven (range, 35–84) years, and most patients were male, had a smoking history, and non-squamous cell carcinoma. Sixty-six (82%) patients received pembrolizumab plus carboplatin/cisplatin and pemetrexed (Table 1). Thirty-seven patients (46%) had cancer cachexia. Patients with cancer cachexia had a significantly higher frequency of ECOG-PS 1 and PD-L1 TPS $\geq 50\%$ than patients without cancer cachexia (86% vs. 63%, *P* = 0.016).

Table 1
Characteristics of Patients

	Total (n = 80)	Cachexia (n = 37)	Non-Cachexia (n = 43)	<i>P</i>
Age (range)	67 (35–86)	67 (36–86)	68 (35–79)	0.671
Sex				0.142
Male	61 (76%)	31 (84%)	30 (70%)	
Female	19 (24%)	6 (16%)	13 (30%)	
ECOG-PS				0.016
0	21 (26%)	5 (14%)	16 (37%)	
1	59 (74%)	32 (86%)	27 (63%)	
Smoking Status				0.271
Ever	70 (88%)	34 (92%)	36 (84%)	
Never	10 (12%)	3 (8%)	7 (16%)	
Histology				0.908
Non-Squamous	71 (89%)	33 (91%)	38 (88%)	
Squamous	9 (11%)	4 (9%)	5 (12%)	
PD-L1 TPS				0.053
< 50%	11 (14%)	9 (24%)	2 (5%)	
1–49%	31 (39%)	14 (38%)	17 (39%)	
≤ 1%	30 (37%)	10 (27%)	20 (47%)	
Unknown	8 (10%)	4 (11%)	4 (9%)	
BMI				0.221
BMI ≥ 25	13 (16%)	4 (11%)	9 (21%)	
BMI < 25	67 (84%)	33 (89%)	34 (79%)	
Stage				0.142
IIIB / IV	61 (76%)	31 (84%)	30 (70%)	

Significant *P*-values are shown in bold type. ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD-L1, programmed cell death protein ligand 1; PD-1, programmed death-1; TPS, tumour proportion score; BMI, Body mass index; CBDCA, carboplatin; PEM, pemetrexed; Pembro, pembrolizumab; CDDP, cisplatin; nab-PTX, nab-paclitaxel; PTX, paclitaxel; Atezo, atezolizumab; BEV, bevacizumab.

	Total (n = 80)	Cachexia (n = 37)	Non-Cachexia (n = 43)	<i>P</i>
Recurrence	19 (24%)	6 (16%)	13 (30%)	
CNS Metastases	23 (29%)	12 (32%)	11 (25%)	0.500
PD-1/PD-L1 + Chemotherapy				0.722
Pembro + CBDCA + PEM	33 (41%)	14 (38%)	19 (44%)	
Pembro + CDDP + PEM	33 (41%)	16 (43%)	17 (39%)	
Pembro + CBDCA + nab-PTX	8 (10%)	3 (8%)	5 (12%)	
Pembro + CBDCA + PTX	1 (1%)	1 (3%)	0	
Atezo + CBDCA + nab-PTX	4 (5%)	2 (5%)	2 (5%)	
Atezo + CBDCA + PTX + BEV	1 (1%)	1 (3%)	0	
Significant <i>P</i> -values are shown in bold type. ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD-L1, programmed cell death protein ligand 1; PD-1, programmed death-1; TPS, tumour proportion score; BMI, Body mass index; CBDCA, carboplatin; PEM, pemetrexed; Pembro, pembrolizumab; CDDP, cisplatin; nab-PTX, nab-paclitaxel; PTX, paclitaxel; Atezo, atezolizumab; BEV, bevacizumab.				

3.2. Efficacy

The objective response rate was 41% (95% confidence interval [CI]: 32–52), and the disease control rate was 73% (95% CI: 61–82) in all patients. Patients with cancer cachexia tended to have a lower objective response rate than those without cancer cachexia (30% vs. 51%, $P = 0.052$). Patients with cancer cachexia had a significantly lower disease control rate than patients without cancer cachexia (57% vs. 86%, $P = 0.003$).

Among the 80 patients, 58 (73%) had disease progression at the cut-off date. The median follow-up time for the study was 20.1 months. Among all patients in this study, the median PFS was 7.3 months (95% CI: 4.8–9.4). The results showed that patients with cancer cachexia had shorter PFS than those without cachexia (5.2 vs. 9.4 months, $P = 0.037$, Fig. 2). The Cox proportional-hazard ratio (95% CI) of cancer cachexia was 1.77 (1.01–3.10) for PFS after adjustments for ECOG-PS, PD-L1 TPS, histology, and CNS metastases (Table 2).

Table 2
 Predictor for Efficacy in PD-1 /PD-L1 inhibitors plus Chemotherapy

PFS	Univariate Analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Cachexia vs. Non-Cachexia	1.72	1.02–2.91	0.040	1.77	1.01–3.10	0.044
PD-L1 TPS ≥ 50% vs. <50% or unknown	0.95	0.41–2.23	0.922	0.68	0.28–1.66	0.407
BMI ≥ 25 vs. BMI < 25	1.09	0.56–2.13	0.778			
Age < 75 vs ≥ 75	0.62	0.36–1.37	0.210			
Female vs. Male	0.70	0.36–1.37	0.309			
Smoking No vs. Yes	0.70	0.27–1.75	0.439			
Non-Squamous vs. Squamous	0.65	0.30–1.39	0.271	0.50	0.22–1.10	0.088
ECOG PS 1 vs. 0	1.42	0.78–2.60	0.248	1.23	0.65–2.35	0.512
CNS metastases Yes vs. No	1.45	0.83–2.53	0.190	1.51	0.83–2.75	0.167

PFS, progression free survival; HR, hazard ratio; PD-L1, programmed cell death protein ligand 1; PD-1, programmed death-1; TPS, tumour proportion score; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CNS, central nervous system.

3.3. Survival outcomes

Among the 80 patients, 36 (45%) died at the cut-off date. Among all patients in this study, the median OS was 17.3 months (95%CI: 13.3–not reached). The results showed that patients with cancer cachexia had shorter OS than those without cachexia (10.8 vs. 23.9 months, $P=0.001$; Fig. 3). After adjusting for ECOG-PS, PD-L1 TPS, histology, and CNS metastasis, the Cox proportional hazard ratio of cancer cachexia for OS was 2.90 (95% CI 1.40-6.00) (Table 3).

Table 3
Prognostic factor in PD-1 /PD-L1 inhibitors plus Chemotherapy

OS	Univariate Analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Cachexia vs. Non-Cachexia	2.96	1.47–5.97	0.002	2.90	1.40–6.00	0.004
PD-L1 TPS ≥ 50% vs. <50% or unknown	1.55	0.59–4.05	0.364	1.02	0.37–2.79	0.966
BMI ≥ 25 vs. BMI < 25	0.79	0.33–1.92	0.616			
Age < 75 vs ≥ 75	0.86	0.34–2.32	0.766			
Female vs. Male	0.53	0.22–1.30	0.170			
Smoking No vs. Yes	0.85	0.30–2.41	0.758			
Non-Squamous vs. Squamous	0.39	0.16–0.91	0.031	0.29	0.11–0.73	0.009
ECOG PS 1 vs. 0	0.67	0.30–1.47	0.314	1.46	0.61–3.49	0.386
CNS metastases Yes vs. No	1.31	0.66–2.61	0.434	1.19	0.56–2.56	0.641
OS, overall survival; HR, hazard ratio; PFS, progression free survival; PD-L1, programmed cell death protein ligand 1; PD-1, programmed death-1; TPS, tumour proportion score; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CNS, central nervous system.						

3.4. Safety

No patient in the study experienced treatment-related adverse events (AEs) leading to death. The occurrence of AEs that led to discontinuation of PD-1/PD-L1 inhibitors plus chemotherapy was not significantly different in patients with cancer cachexia than those without cancer cachexia (35% vs. 21%, $P=0.555$). Furthermore, no significant differences in grade 3 or higher non-hematologic AEs (11% vs. 7%, $P=0.545$) and immune-related AEs (11% vs. 7%, $P=0.545$) were found between patients with cancer cachexia and those without cancer cachexia. Rash occurred more frequently in patients without cancer cachexia than in those with cancer cachexia (19% vs. 8%, $P=0.014$). Adrenal insufficiency, hypothyroidism/hyperthyroidism, infusion reaction, and nephritis only occurred in patients without cachexia (Supplementary Table 1).

4. Discussion

To the extent of our knowledge, the present study provides the first evaluation of the impact of cancer cachexia on the survival outcome of PD-1/PD-L1 inhibitors plus chemotherapy. We found that cancer cachexia independently adversely affected survival outcomes for PD-1/PD-L1 inhibitors plus chemotherapy in analyses that included other clinical constraints. However, cancer cachexia did not affect the safety of PD-1/PD-L1 inhibitors plus chemotherapy. Several previous studies have demonstrated that cancer cachexia or sarcopenia adversely affects the clinical outcome of PD-1 or PD-L1 inhibitor monotherapy. [11, 12] Meanwhile, no previous studies have evaluated the efficacy of PD-1/PD-L1 inhibitor plus chemotherapy, the current standard primary treatment for advanced NSCLC, separately in the existence of cancer cachexia, as shown in this study. Although cancer cachexia has an adverse impact on clinical outcomes among patients with advanced NSCLC, it has not been incorporated as a stratifying factor in most clinical trials. Moreover, it is under-recognized at the time of first-line treatment in clinical practice. [1–6]

Past studies demonstrated a negative impact on the outcome of chemotherapy. [16–18] Cancer cachexia not only reduces patients' tolerance to chemotherapy but also decreases objective tumour response, PFS, and OS in patients who have received platinum-based chemotherapy. [19] Cisplatin both directly and indirectly inhibits protein synthesis and promotes protein degradation in skeletal muscles. [20] Significant losses in body weight, muscle mass, and nutritional status are often observed in patients with cancer treated with cisplatin, primarily due to muscle wasting and chemotherapy-induced anorexia. [21]

More importantly, recent basic and clinical studies have revealed multiple potential cancer cachexia mechanisms negatively affecting tumour immunity. [22] Several studies have demonstrated that cancer cachexia induces various pro-inflammatory cytokines, including interleukin (IL)-6, IL-1 β , and tumour necrosis factor (TNF) α . Basic research has demonstrated that IL-6 causes elevation of glycol-corticoids and suppression of cytotoxic T-cells. [23] Basic research has shown that IL-1 β adversely influences tumour-infiltrating T-cells, mainly due to inducing myeloid-derived suppressor cells. [24] Furthermore, TNF- α also suppresses tumour-infiltrating lymphocytes (TILs), a key regulator of PD-1/ PD-L1 inhibitors, resulting in decreased efficacy. [25] All these mechanisms suggest that cancer cachexia is not only an adverse prognostic factor but also an essential predictor for the effectiveness of PD-1/PD-L1 inhibitors. Thus, the difference in therapeutic outcome of PD-1/PD-L1 plus chemotherapy according to the presence of cancer cachexia may be further accentuated.

To fully benefit from the treatment of PD1/PD-L1 inhibitors plus chemotherapy, it may be necessary to simultaneously treat and evaluate cancer cachexia at the time of initial treatment. Anamorelin has high affinity and selectivity as a ghrelin receptor agonist and acts through the insulin-like growth factor pathway. [26] Two pivotal clinical studies have provided evidence that anamorelin significantly increases lean body mass. [27] The reasons anamorelin did not improve survival may be that patients received only the best supportive care and that most patients had already received multiple chemotherapy regimens. Recently, anamorelin was approved for marketing authorization to treat cancer cachexia in Japan. [28] Considering the therapeutic effect of anamorelin in cancer cachexia, the therapeutic approach combining anamorelin with PD-1/PDL1 inhibitors may reduce the adverse effects of cancer cachexia. Further basic

and clinical research may be required to validate our new hypothesis regarding the potential benefits of anamorelin.

The present study is subject to several limitations. First, this study is retrospective, which fails to account for unknown confounding factors, and the small sample size could have affected the study's statistical power. Second, we did not evaluate biomarkers of cancer cachexia, including IL-1 β , IL-6, and TNF- α . [23–25] Third, the small size of the population at a single cancer centre in Japan limits our results' applicability to the overall population.

Additionally, unlike the results of previous studies, a high expression of PD-L1 TPS was not an independent predictive factor for the efficacy of PD-1/PD-L1 inhibitors plus chemotherapy in this study. At our institution, patients with high PD-L1 expression are mainly treated with pembrolizumab monotherapy. Patients with a high tumour burden or more rapidly progressing tumours are treated with PD-1/PD-L1 inhibitors plus chemotherapy. We believe that this bias in treatment selection led to the absence of a difference in the efficacy of PD-1/PD-L1 inhibitors plus chemotherapy concerning PD-L1 TPS. Furthermore, this study did not include skeletal muscle mass assessment, an essential component of cancer cachexia. Further prospective studies with a more significant number of patients are warranted to validate the present study results.

In conclusion, our findings indicate that pre-treatment cancer cachexia may reduce the efficacy and shorten the survival time in patients receiving PD-1/PD-L1 inhibitors plus chemotherapy. Early evaluation and intervention for cancer cachexia might improve oncological outcomes in patients with advanced NSCLC.

Declarations

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

Dr. Taichi Miyawaki - Declarations of interest: none.

Dr. Naito - Declarations of interest: none.

Dr. Yabe - Declarations of interest: none.

Dr. Kodama - Declarations of interest: none.

Dr. Nishioka - Declarations of interest: none.

Dr. Eriko Miyawaki - Declarations of interest: none.

Dr. Mamesaya reports personal fees from AstraZeneca KK, Pfizer Japan, Inc., personal fees from Chugai Pharmaceutical Co., Ltd., grants and personal fees from Boehringer Ingelheim, personal fees from MSD K.K., personal fees from TAIHO PHARMACEUTICAL CO., LTD., personal fees from ONO PHARMACEUTICAL CO., LTD., outside the submitted work.

Dr. Kobayashi reports personal fees from Eli Lilly K.K, personal fees from Taiho Pharmaceutical, personal fees from AstraZeneca, outside the submitted work.

Dr. Omori reports personal fees from Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical, AstraZeneca K.K., Boehringer Ingelheim, Taiho Pharmaceutical, and MSD, which are unrelated to the submitted work.

Dr. Wakuda reports grants and personal fees from Chugai Pharmaceutical Co., Ltd., personal fees from Taiho Pharmaceutical, personal fees from Boehringer Ingelheim, personal fees from Eli Lilly K.K., personal fees from Ono Pharmaceutical, personal fees from MSD, grants from Novartis, grants from Abbvie, grants and personal fees from AstraZeneca, outside the submitted work.

Dr. Ono reports grants from Taiho Pharmaceutical, grants from Ono Pharmaceutical, grants from Chugai Pharmaceutical Co., Ltd., grants from Novartis Pharma K.K., outside the submitted work.

Dr. Kenmotsu reports grants and personal fees from Chugai Pharmaceutical Co, Ltd., personal fees from Ono Pharmaceutical Co, Ltd. , personal fees from Boeringer Ingelheim, personal fees from Eli Lilly K.K, personal fees from Kyowa Hakko Kirin Co., Ltd., personal fees from Bristol-Myers Squibb, personal fees from MSD, grants and personal fees from Novartis Pharma K.K., grants and personal fees from Daiichi-Sankyo Co., Ltd., grants and personal fees from AstraZeneca K.K., personal fees from Pfizer, personal fees from Taiho Pharma, outside the submitted work.

Dr. Murakami reports personal fees from AstraZeneca K.K., Ono Pharmaceutical, Bristol-Myers Squibb Japan, Chugai Pharmaceutical Co., Ltd., Pfizer Inc., Novartis Pharma K.K., Boehringer Ingelheim, Taiho Pharmaceutical, Eli Lilly K.K., and MSD, which are unrelated to the submitted work.

Dr. Mori - Declarations of interest: none.

Dr. Harada reports personal fees from Daiichi Sankyo Pharmaceutical Co. during the conduct of the study as well as personal fees from Daiichi Sankyo Pharmaceutical Co., AstraZeneca K.K., Brain Labo Co., and Chugai Pharmaceutical Co. and grants from the Japan Agency for Medical Research and Development and the National Cancer Center Research and Development Fund, which are unrelated to the submitted work.

Dr. Kazuhisa Takahashi reports grants and personal fees from AstraZeneca K.K., Pfizer Japan, Inc., Eli Lilly K.K., MSD, and Boehringer Ingelheim as well as grants from Takeda Pharmaceutical Company Ltd., Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., KYORIN Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., GlaxoSmithKline Consumer Healthcare Japan K.K., SHIONOGI & CO., LTD., and Novartis Pharma K.K., which are unrelated to the submitted work.

Dr. Toshiaki Takahashi reports grants and personal fees from AstraZeneca KK, Pfizer Japan, Inc., grants and personal fees from Eli Lilly Japan K.K., grants and personal fees from Chugai Pharmaceutical Co., Ltd., grants and personal fees from Ono Pharmaceutical Co., Ltd., grants and personal fees from MSD K.K., grants and personal fees from Boehringer Ingelheim Japan, Inc., grants and personal fees from Pfizer Japan, Inc., personal fees from Roche Diagnostics K.K., outside the submitted work.

Author contributions

TM and TN wrote the manuscript and researched data. TN reviewed and edited the manuscript. KM is a professional biostatistician and responsible for statistical analysis. All authors reviewed, approved the final version of the manuscript, and certified that they comply with the ethical guidelines for publishing in the Supportive care in Cancer.

Availability of data and material

All data and material are available on reasonable request.

Ethics approval

The ethical review board of our institution approved the study (registration no. J2020-176-2020-1). All procedures performed in studies involving human participants were in accordance with 1964 Helsinki declaration and its later amendments or with comparable ethical standards.

Consent to participate

For this type of study, formal consent is not required. We have also applied an opt-out method to obtain consent for this study by posting a document about this study. The document has been approved by the institutional ethics review board of Shizuoka Cancer Center.

Consent for publication

Not applicable.

Code availability

Not applicable.

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Figures

Figure.1

Patient flow diagram

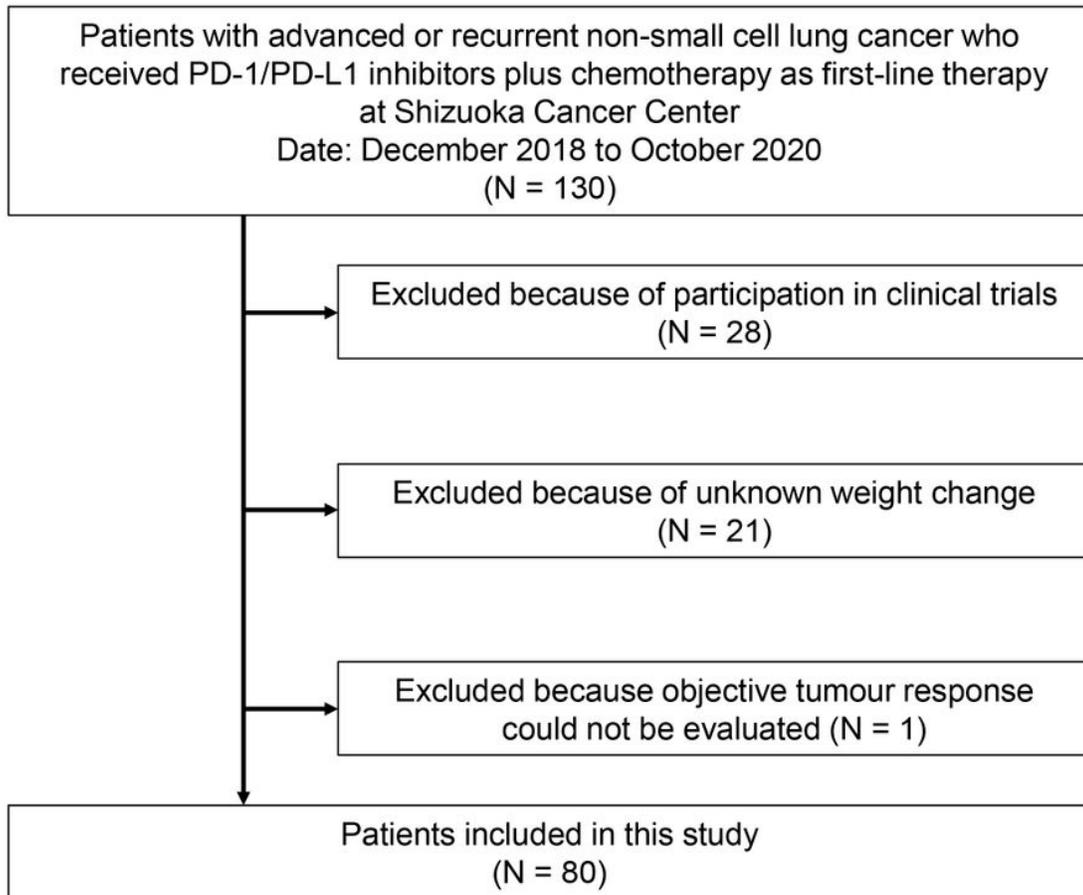


Figure 1

Study flowchart. PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

Figure. 2

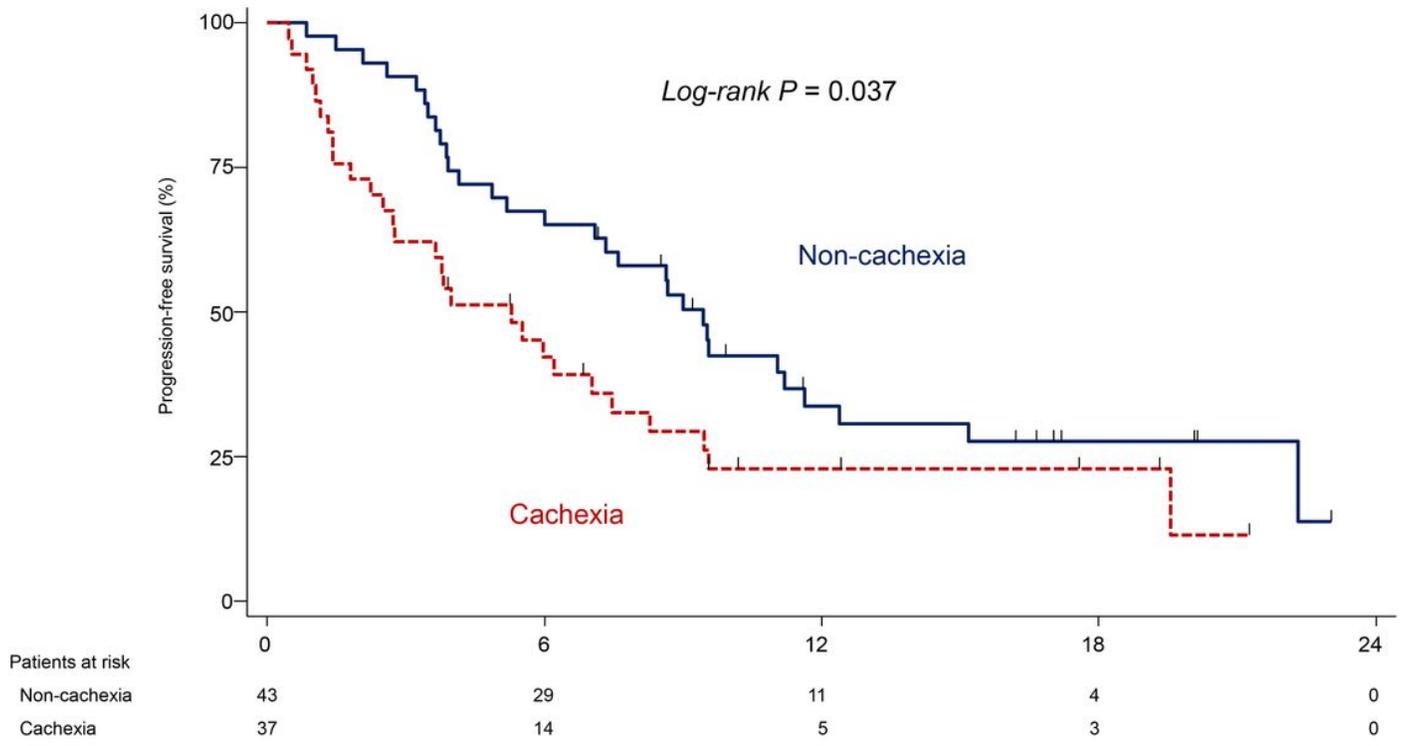


Figure 2

Kaplan-Meier curves for progression-free survival according to the presence of cancer cachexia (non-cachexia vs. cachexia). The P-values were calculated using the log rank test. The small vertical lines on the curve indicate patients who were censored.

Figure. 3

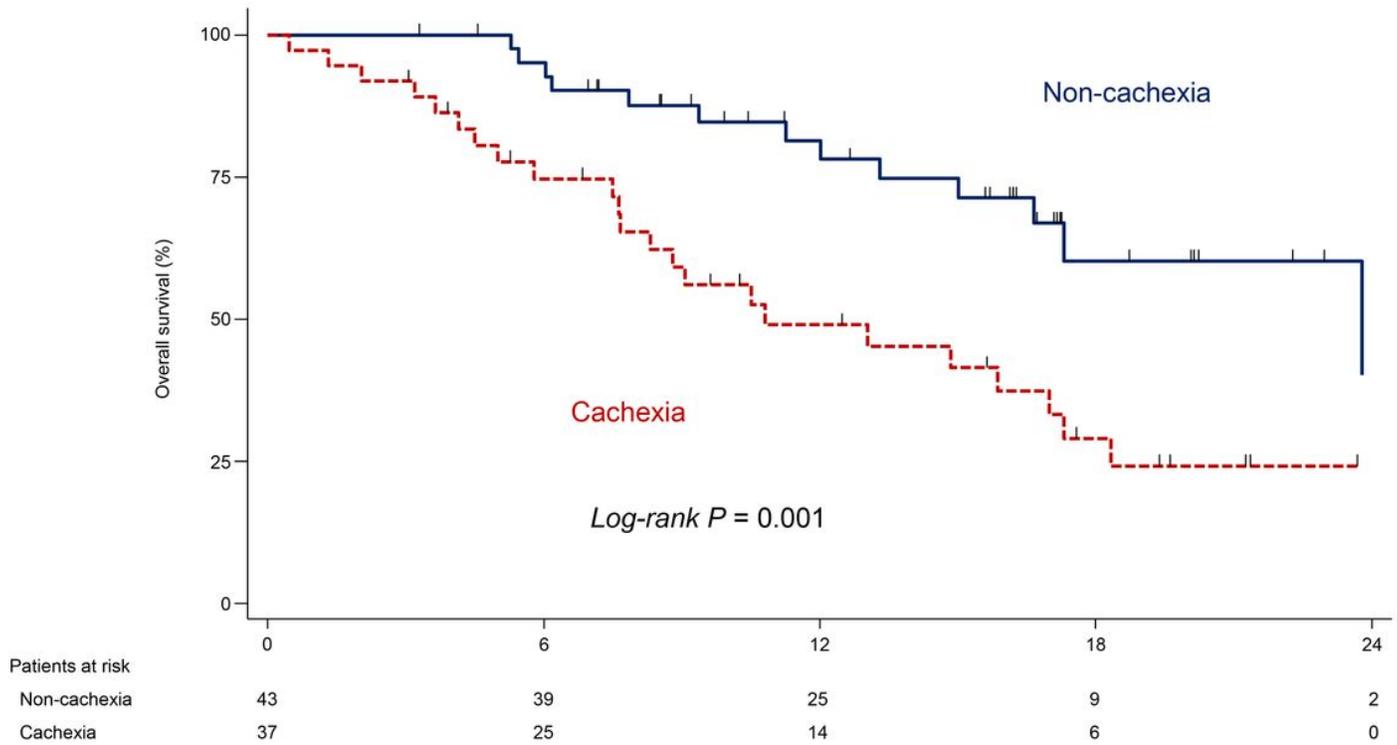


Figure 3

Kaplan-Meier curves for overall survival according to the presence of cancer cachexia (non-cachexia versus cachexia). The P-values were calculated using the log-rank test. The small vertical lines on the curve indicate patients who were censored.

Supplementary Files

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