ORIGINAL ARTICLE

Evaluation of osimertinib efficacy according to body surface area and body mass index in patients with non-small cell lung cancer harboring an *EGFR* mutation: A prospective observational study

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Abstract

Background: Osimertinib is recommended for non-small cell lung cancer (NSCLC) patients with *EGFR* mutation; however, it is unclear whether body size variables affect the efficacy of osimertinib in such patients. This study assessed the potential effect of body surface area (BSA) and body mass index (BMI) on osimertinib chemotherapy in patients with T790M-positive advanced NSCLC who progress on prior *EGFR*-tyrosine kinase inhibitors (TKIs).
Methods: We conducted a prospective observational cohort study. Median BSA and BMI were used as cut-off values to evaluate the impact of body size variables on osimertinib chemotherapy.
Results: The median BSA and BMI of 47 patients were 1.50 m^2 and 21.5 kg/m^2, respectively. Clinical outcomes did not significantly differ between the high and low BSA groups, with response rates of 59.1% and 56.0% ($P = 0.83$) and progression-free survival (PFS) of 7.6 and 9.1 months ($P = 0.69$), respectively. Similarly, there were no significant differences between the high and low BMI groups relative to response rates, which were 60.8% and 54.1% ($P = 0.64$), respectively, and PFS, which was 7.6 months in both groups ($P = 0.38$). No significant differences were observed among toxicity profiles in relation to BSA or BMI. Multivariate analysis identified better performance status, young age, and *EGFR* exon 19 deletion as independent favorable predictors of PFS.
Conclusion: The efficacy of osimertinib does not significantly vary relative to body size variables of patients with T790M-positive NSCLC who progress on prior *EGFR*-TKIs.

Introduction

Lung cancer is a major cause of cancer death. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers.[1] Targeted therapies are currently being developed to improve efficacy in driver-oncogene positive NSCLC patient populations. Small-molecule tyrosine kinase inhibitors (TKIs) that target *EGFR* have been introduced clinically for the treatment of NSCLC. Meta-analyses have clearly indicated improved progression-free survival (PFS) and response rates in patients with *EGFR* mutations administered *EGFR*-TKI therapy including gefitinib, erlotinib, and afatinib, compared to patients administered chemotherapy with cytotoxic drugs.[2–5] Based on these results, *EGFR*-TKIs have become the standard regimen for

patients with advanced NSCLC harboring an *EGFR* mutation. In addition, *EGFR*-TKIs combined with chemotherapy in NSCLC patients with *EGFR* mutations is reported achieve longer survival and tolerable side effects.[6–8] However, despite initial responses to *EGFR*-TKI, the majority of patients will experience disease progression within two years as a result of acquired resistance.[9–17] In approximately 60% of patients, the mechanism of acquired resistance is the development of an additional *EGFR* mutation, *EGFR* T790M.[16] Osimertinib is a mono-anilino-pyrimidine compound that irreversibly and selectively targets *EGFR*-TKI-sensitizing and T790M resistant mutant forms of *EGFR*, while sparing wild-type *EGFR*.[18–20] A Phase I/II AURA trial was conducted to determine the safety and efficacy of osimertinib in patients with advanced NSCLC who experience disease progression after previous treatment with *EGFR*-TKIs.[21] Osimertinib showed high efficacy in patients with T790M mutation, with an objective response rate (ORR) of 61% and median PFS of 9.6 months. To confirm results of the single-arm, Phase I/II AURA trial, a randomized, Phase III trial (AURA3) was conducted that demonstrated the superiority of osimertinib treatment over standard chemotherapy with platinum and pemetrexed in patients with *EGFR*-mutated and centrally confirmed T790M-positive advanced NSCLC who experienced disease progression after first-line *EGFR*-TKI therapy.[22] Analysis of the primary endpoint indicated a significantly longer PFS in patients administered osimertinib compared to those treated with platinum chemotherapy. This result established the role of osimertinib as the standard-of-care for patients harboring the T790M resistance mutation who progress on first-line *EGFR*-TKIs. Because the standard dose of osimertinib was determined as 80 mg/day, a uniform dosage of 80 mg/day is prescribed, regardless of body size. Although dose adjustments based on body surface area (BSA) have been made in chemotherapy with cytotoxic agents, it is unknown whether body size variables, such as BSA or body mass index (BMI), affect the efficacy of osimertinib therapy in NSCLC patients who carry an *EGFR* mutation.

The objective of this study was to determine whether BSA and BMI affect the efficacy of osimertinib in patients with advanced NSCLC harboring a T790M mutation.

Methods

Patient selection

We conducted a prospective observational cohort study at Kitasato University Hospital between January 2017 and April 2018 to evaluate the efficacy and safety of osimertinib in patients with T790M-positive advanced NSCLC who experienced disease progression after first-line *EGFR*-TKI

therapy including gefitinib, erlotinib, and afatinib. The eligibility criterion of this study was histologically or cytologically confirmed NSCLC and stage IIIB/IV disease or recurrence according to the new Union for International Cancer Control criteria, version 8. We excluded patients who did not have at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[23] Patient characteristics, including age at diagnosis, gender, Eastern Cooperative Oncology Group performance status (PS) at the start of the osimertinib treatment, smoking status, clinical stage, tumor histology, BSA, BMI, brain metastasis status, number of metastatic lesions, and number of previous chemotherapy regimens, were identified by chart review. Patients were classified according to smoking status as current smokers, former light smokers (having smoked a total of ≤ 10 pack-years plus smoking cessation at least 15 years previously), and never smokers (a lifetime history of having smoked < 100 cigarettes). We used the following formula to calculate BSA: BSA (m^2) = (body weight $[kg])^{0.425}$ × (height $[cm])^{0.725}$ × 0.007184. The BMI kg/m^2 at the start of treatment was defined as the weight (kg) divided by the height (m) squared.

All patients provided written informed consent. The Kitasato University Hospital institutional ethics review board approved the study. After obtaining written consent, the patients were treated with 80 mg of osimertinib per subject until disease progression or unacceptable adverse events occurred.

Analysis of *EGFR* mutations

A sample of the primary tumor, a metastatic lesion, or pleural effusion fluid was used as a specimen to test for *EGFR* mutation via the peptide nucleic acid-locked nucleic acid PCR clamp method and the Cobas *EGFR* Mutation Test. Tumor biopsy cytology specimens, along with plasma specimens recovered by liquid biopsy, were tested for *EGFR* T790M status using the Cobas *EGFR* Mutation Test.

Response and toxicity assessment

After the initiation of osimertinib treatment, a computed tomography (CT) scan of the chest and abdomen was carried out every two to three months or at more frequent intervals. Positron emission tomography (PET) or bone scintigraphy and CT or magnetic resonance imaging (MRI) of the cranium were performed when patients exhibited significant symptoms associated with tumor lesions or at six-month intervals. Response to treatment was re-evaluated by two investigators according to RECIST 1.1.[23] Medical records were reviewed to evaluate the toxicities experienced by all patients. Toxicities were graded

according to the National Cancer Institute Common Toxicity Criteria version 4 grading system.

Statistical analysis

The Fisher's exact test was used to assess the distributions of categorical characteristics according to whether the patients' BSA was ≥ 1.50 m^2 (high-BSA group) or < 1.50 m^2 (low-BSA group), as well as according to whether the patients' BMI was ≥ 21.5 (high-BMI group) or < 21.5 kg (low-BMI group). The toxicities were also compared according to the median BSA and BMI by Fisher's exact test. PFS was measured from the start of gefitinib therapy to treatment failure (death, documentation of disease progression, or appearance of unacceptable toxicity) or the date the final follow-up examination was censored. Overall survival (OS) was defined as the interval between the start of gefitinib therapy to death from any cause or the date of censoring. The survival curves were plotted using the Kaplan–Meier method and differences according to BSA and BMI were analyzed using the log-rank test. Cox's proportional hazard models of variables including age, gender, smoking status, PS, stage, brain metastasis status, type of *EGFR* mutation, number of prior regimens, BSA, and BMI were used to predict the hazard rates for PFS. The differences in response rates according to BSA and BMI were compared by Fisher's exact test. $P < 0.05$ was used as the criterion for statistical significance. All statistical analyses were performed using SPSS version 17.0.

Results

Patient characteristics

A total of 47 NSCLC patients treated with osimertinib between May 2016 and April 2018 were included in the final analysis. The basic characteristics of the patients were: 66% female, median age 73 years, and 66% had a good PS (0 or 1) (Table 1). The patients suffered from adenocarcinoma (47 patients, 100%) and stage IV disease or postoperative recurrence (47 patients, 100%). The median BSA was 1.50 m^2 (range: 1.16–1.79 m^2) and the median BMI was 21.5 kg/m^2 (range: 14.0–28.2 kg/m^2). There were significantly higher percentages of men (87% vs. 35%, $P < 0.001$), non-elderly (e.g. <75) patients (72% vs. 44%, $P < 0.001$), patients with good PS (62% vs. 34%, $P = 0.03$), smokers (79% vs. 42%, $P = 0.024$), and patients with L858R point mutation (66% vs. 29%, $P = 0.015$) in the high-BSA (BSA ≥ 1.5 m^2) group than in the low-BSA (BSA < 1.5 m^2) group (Table 2). Regarding the BMI, there were significantly higher percentages of patients with a good PS (62% vs. 27%, $P = 0.01$) and L858R point mutation (61% vs. 29%, $P = 0.048$) in the high-BMI

Table 1 Patient characteristics

Characteristics	N = 47 (%)
Age (years), median, range	73 (42–91)
Gender	
Male/Female	16 (34)/31 (66)
Performance status	
0–1/2–4	31 (66)/16 (34)
EGFR genotype	
Exon 19 deletion/L858R	30 (64)/17 (36)
Histology	
Adenocarcinoma	47 (100)
Stage	
IV or recurrence	6 (13)/41 (87)
Smoking status	
Current smoker	16 (34)
Never or former light smoker	31 (66)
Type of EGFR-TKI	
Gefitinib/Erlotinib/Afatinib	33 (70)/9 (19)/5 (11)
BSA (m^2)	
≥ 1.5	25 (53)
< 1.5	22 (47)
BMI (kg/m^2)	
≥ 21.5	24 (51)
< 21.5	23 (49)
Brain metastasis	
Positive/Negative	16 (34)/31 (66)
Number of metastatic lesions	
1	18 (38)
≥ 2	29 (62)
Number of prior regimens (median, range)	2 (1–6)
1	20 (42)
≥ 2	27 (58)

BMI, body mass index; BSA, body surface area; TKI, tyrosine kinase inhibitor.

(BMI ≥ 21.5 kg/m^2) group than in the low-BMI (BMI < 21.5 kg/m^2) group (Table 3).

Response to osimertinib according to body surface area (BSA) and body mass index (BMI)

An objective response was obtained in 27 of the 47 patients, indicating an objective response rate (ORR) of 57.4% (95% confidence interval [CI] 43.3–71.5%) (Table 4). We used the median BSA and BMI values as the cutoff values to evaluate the impact of body size on the efficacy of osimertinib monotherapy. The response rate was 59.1% (95% CI 38.6–79.6%) in the low-BSA group and 56% (95% CI 36.5–75.5%) in the high-BSA group, indicating no statistically significant difference ($P = 0.83$). The response rate was 60.8% (95% CI 40.8–80.8%) in the low-BMI group and 54.1% (95% CI 34.2–74.0%) in the high-BMI group, also indicating no statistically significant difference ($P = 0.64$).

Table 2 Patient characteristics in the high-BSA (BSA ≥ 1.50 m^2) group

Characteristics	N (%)		
	BSA < 1.5	BSA ≥ 1.5	P
Gender			< 0.001
Male	2 (13)	14 (87)	
Female	20 (65)	11 (35)	
Age (years)			< 0.001
< 75	8 (28)	21 (72)	
≥ 75	14 (78)	4 (22)	
Performance status			0.03
0–1	12 (38)	20 (62)	
2–4	10 (67)	5 (34)	
Smoking status			0.024
Current smoker	3 (21)	11 (79)	
Never or former light smoker	19 (58)	14 (42)	
Stage			0.60
Postoperative recurrence	3 (50)	3 (50)	
Stage IV	19 (46)	22 (54)	
Brain metastasis			0.39
Positive	6 (38)	10 (62)	
Negative	16 (52)	15 (48)	
EGFR genotype			0.015
Exon 19 deletion	10 (34)	20 (66)	
L858R	12 (71)	5 (29)	
Prior regimens			0.25
1	11 (55)	9 (45)	
≥ 2	11 (41)	16 (59)	

BSA, body surface area.

Table 3 Patient characteristics in the high-BMI (BMI ≥ 21.5 kg/m^2) group

Characteristics	N (%)		
	BMI < 21.5	BMI ≥ 21.5	P
Gender			0.21
Male	6 (34)	10 (66)	
Female	17 (55)	14 (45)	
Age (years)			0.16
< 75	12 (41)	17 (59)	
≥ 75	11 (61)	7 (39)	
Performance status			0.01
0–1	11 (38)	20 (62)	
2–4	12 (73)	4 (27)	
Smoking status			0.59
Current smoker	7 (50)	7 (50)	
Never or mild former light smoker	16 (48)	17 (52)	
Stage			0.65
Postoperative recurrence	3 (50)	3 (50)	
Stage IV	20 (48)	21 (52)	
Brain metastasis			0.46
Positive	9 (53)	8 (47)	
Negative	14 (47)	16 (53)	
EGFR genotype			0.048
Exon 19 deletion	10 (33)	20 (67)	
L858R	13 (76)	4 (24)	
Prior regimens			0.57
0	10 (50)	10 (50)	
≥ 1	13 (48)	14 (52)	

BMI, body mass index.

Toxicities

The most common non-hematologic toxicities of any grade were diarrhea (18 patients, 38.3%), skin rash (15 patients, 31.9%), and fatigue (10 patients, 21.3%). Grade 3 diarrhea occurred in two patients. Regarding hematologic toxicities of any grade, thrombocytopenia (10 patients, 21.3%), anemia (7 patients, 14.9%) and leukopenia (6 patients, 12.8%) were observed. Grade 3 thrombocytopenia occurred in one patient. A comparison of toxicities in relation to BSA and BMI is shown in Tables 5 and 6, respectively. There were no significant differences in the frequencies of any of the toxicities relative to BSA or BMI.

Survival

The cutoff date of the survival data update was the end of November 2018. The median follow-up period at the time of survival analysis was 10.6 months. The median PFS and survival of the entire patient population was 7.6 (95% CI 6.4–8.8) and 14.7 (95% CI 9.1–20.5) months, respectively (Fig 1). The median PFS rates in the low-BSA and high-BSA groups were 9.1 (95% CI 3.7–14.5) and 7.6 (95% CI 6.7–8.5) months, respectively, indicating statistically non-

significant differences (*P* = 0.69) (Fig 2a). The median PFS rates in the low-BMI and high-BMI groups were 7.6 (95% CI 2.0–13.2) and 7.6 (95% CI 6.6–8.6) months, respectively, indicating statistically non-significant differences (*P* = 0.38) (Fig 2b). Univariate analysis identified PS, brain metastasis status, and the number of prior regimens as significantly predictive of PFS, while multivariate analysis identified patient age, PS, and *EGFR* genotype as independent predictors of PFS (Table 7). We evaluated 1.40 and 1.60 m^2 as alternative BSA cutoff values in the univariate analysis, but none of the differences in PFS were significant (BSA < 1.40 m^2: hazard ratio [HR] 0.83, *P* = 0.58; BSA < 1.60 m^2: HR 0.076, *P* = 0.43). We also evaluated 20.0 and 23.0 kg/m^2 as alternative BMI cutoff values in the univariate analysis and did not observe any significant differences in PFS (BMI < 20 kg/m^2: HR 0.84, *P* = 0.63; BMI < 23 kg/m^2: HR 1.13, *P* = 0.71). In patients with good PS scores, the median PFS values in the low-BSA and high-BSA groups were 10.2 (95% CI 1.9–18.5) and 7.8 (95% CI 6.1–9.5) months, respectively, without any significant differences (*P* = 0.64). The median PFS rates in the low-BMI and high-BMI groups were 10.2 (95% CI 0.1–22.9) and 7.8 (95% CI 6.3–9.3) months, respectively, indicating statistically non-significant differences (*P* = 0.63) (Fig 3).

Table 4 Responses to osimertinib therapy

Response	All patients (n = 47)	BSA < 1.5 (n = 22)	BSA ≥ 1.5 (n = 25)	BMI < 21.5 (n = 23)	BMI ≥ 21.5 (n = 24)
Complete response	0	0	0	0	0
Partial response	27	13	14	14	13
Stable disease	12	3	9	3	9
Progressive disease	7	5	2	5	2
Not evaluable	1	1	0	1	0
Response rate	57.4%	59.1%	56.0%	60.8%	54.1%
			$P = 0.83$		$P = 0.64$

BMI, body mass index; BSA, body surface area.

Discussion

In approximately 60% of patients, the mechanism of acquired resistance is the development of an additional *EGFR* mutation, T790M.[13] While osimertinib treatment is recognized as the standard-of-care for patients harboring the T790M resistance mutation who progress on first-line *EGFR*-TKIs, the standard dose of osimertinib is 80 mg/day, a uniform dosage regardless of patients' body size. The results of this prospective observational study show that BSA and BMI have no statistically significant effect on the clinical outcomes of osimertinib monotherapy, including the response rate and PFS, in patients with T790M-positive advanced NSCLC who experience disease progression after

first-line *EGFR*-TKI therapy. To our knowledge, this is the first report to evaluate the relationship between osimertinib treatment and body size in this type of patient. The degree of toxicities, including diarrhea, thrombocytopenia, and skin, was also assessed. The toxicity profiles did not vary significantly among the patients in relation to the BSA or BMI. Because the results for the categorical variables indicated a significantly higher proportion of patients with good PS in the high-BSA and high-BMI groups than in the low-BSA and low-BMI groups, it is reasonable to ascribe this significant difference to the body weight loss caused by disease progression. Moreover, re-evaluation of the PFS results in patients with good PS did not indicate any statistically significant differences in the median PFS relative to

Table 5 Toxicities in the low-BSA (BSA < 1.50 m²) and high-BSA (BSA ≥ 1.50 m²) groups

	All grades			≥ Grade 3		
	BSA ≥ 1.5	BSA < 1.5		BSA ≥ 1.5	BSA < 1.5	
Toxicity	N (%)	N (%)	P	N (%)	N (%)	P
Leukopenia	5 (25%)	1 (4.5%)	0.13	0 (0%)	0 (0%)	
Neutropenia	2 (8%)	1 (4.5%)	0.55	0 (0%)	0 (0%)	
Anemia	4 (16%)	3 (13.6%)	0.57	0 (0%)	0 (0%)	
Thrombocytopenia	7 (28%)	3 (13.6%)	0.20	1 (4.0%)	0 (0%)	0.54
Skin rash	9 (36%)	6 (27.2%)	0.37	0 (0%)	0 (0%)	
Liver dysfunction	3 (12%)	1 (4.5%)	0.35	0 (0%)	0 (0%)	
Diarrhea	9 (36%)	9 (40.9%)	0.48	0 (0%)	2 (9.1%)	0.21
Nausea	3 (12%)	3 (13.6%)	0.79	0 (0%)	0 (0%)	
Anorexia	3 (12%)	4 (18.2%)	0.43	0 (0%)	1 (4.5%)	0.95
Constipation	2 (8%)	1 (4.5%)	0.55	0 (0%)	0 (0%)	
Paronychia	1 (4%)	4 (18.2%)	0.14	0 (0%)	0 (0%)	
Fatigue	8 (32%)	2 (9.1%)	0.07	0 (0%)	0 (0%)	
Dry skin	1 (4%)	1 (4.5%)	0.53	0 (0%)	0 (0%)	
Mucositis oral	3 (12%)	1 (4.5%)	0.35	0 (0%)	0 (0%)	
Neuropathy	0 (0%)	1 (4.5%)	0.95	0 (0%)	0 (0%)	
Conjunctivitis	1 (4%)	2 (9.1%)	0.45	0 (0%)	0 (0%)	
Pneumonitis	3 (12%)	2 (9.1%)	0.56	0 (0%)	0 (0%)	
Ileus	0 (0%)	1 (4.5%)	0.95	0 (0%)	0 (0%)	
Edema	0 (0%)	1 (4.5%)	0.95	0 (0%)	0 (0%)	
Cellulitis	0 (0%)	1 (4.5%)	0.95	0 (0%)	0 (0%)	
Renal dysfunction	3 (12.0%)	0 (0%)	0.28	0 (0%)	0 (0%)	
Fever	1 (4.0%)	0 (0%)	0.54	0 (0%)	0 (0%)	

BSA, body surface area.

Table 6 Toxicities in the low-BMI (BMI < 21.5 kg/m^2) and high-BMI groups (BMI ≥ 21.5 kg/m^2)

| | All grades | | | ≥ Grade 3 | | |
| | BMI ≥ 21.5 | BMI < 21.5 | | BMI ≥ 21.5 | BMI < 21.5 | |
Variable	N (%)	N (%)	*P*	N (%)	N (%)	*P*
Leukopenia	5 (20.8%)	1 (4.3%)	0.10	0 (0%)	0 (0%)	
Neutropenia	2 (8.3%)	1 (4.3%)	0.52	0 (0%)	0 (0%)	
Anemia	3 (12.5%)	4 (17.4%)	0.48	0 (0%)	0 (0%)	
Thrombocytopenia	6 (25.0%)	4 (17.4%)	0.39	1 (4.2%)	0 (0%)	0.51
Skin rash	10(41.2%)	5 (21.7%)	0.12	0 (0%)	0 (0%)	
Liver dysfunction	3 (12.5%)	1 (4.3%)	0.32	0 (0%)	0 (0%)	
Diarrhea	10(41.2%)	8 (34.8%)	0.43	0 (0%)	2 (8.7%)	0.23
Nausea	2 (8.3%)	4 (17.4%)	0.31	0 (0%)	0 (0%)	
Anorexia	2 (8.3%)	5 (21.7%)	0.19	0 (0%)	1 (4.3%)	0.49
Constipation	1 (4.2%)	2 (8.7%)	0.48	0 (0%)	0 (0%)	
Paronychia	4 (16.7%)	1 (4.3%)	0.52	0 (0%)	0 (0%)	
Fatigue	6 (25.0%)	4 (17.4%)	0.39	0 (0%)	0 (0%)	
Dry skin	1 (4.2%)	1 (4.3%)	0.74	0 (0%)	0 (0%)	
Mucositis oral	3 (12.5%)	1 (4.3%)	0.32	0 (0%)	0 (0%)	
Neuropathy	1 (4.2%)	0 (0%)	0.51	0 (0%)	0 (0%)	
Conjunctivitis	1 (4.2%)	2 (8.7%)	0.48	0 (0%)	0 (0%)	
Pneumonitis	2 (8.3%)	3 (13.0%)	0.48	0 (0%)	0 (0%)	
Ileus	0 (0%)	1 (4.3%)	0.49	0 (0%)	0 (0%)	
Edema	0 (0%)	1 (4.3%)	0.49	0 (0%)	0 (0%)	
Cellulitis	0 (0%)	1 (4.3%)	0.49	0 (0%)	0 (0%)	
Renal dysfunction	3 (12.5%)	0 (0%)	0.12	0 (0%)	0 (0%)	
Fever	1 (4.3%)	1 (4.3%)	0.74	0 (0%)	0 (0%)	

BMI, body mass index.

N	PFS (months)	95% CI
47	7.6	6.4–8.8

N	OS (months)	95% CI
47	14.7	9.1–20.5
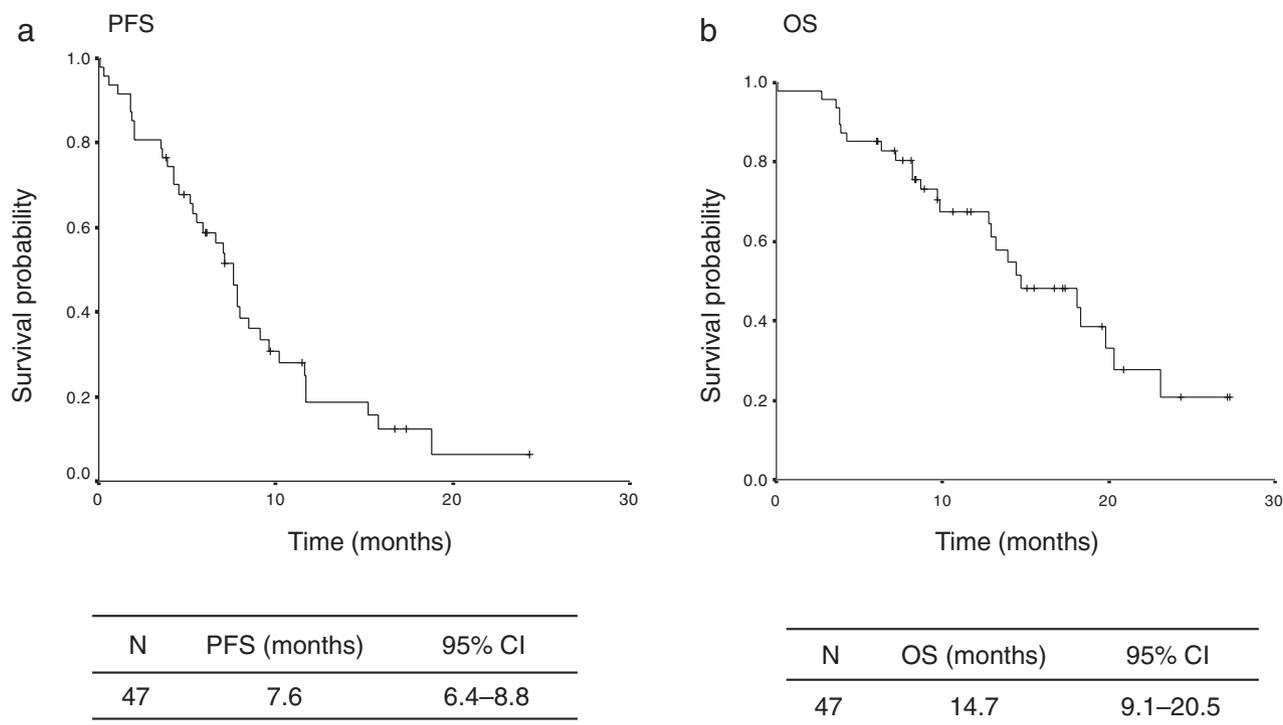
Figure 1 Kaplan–Meier plots of (**a**) progression-free survival (PFS) and (**b**) overall survival (OS). CI, confidence interval.

a

BSA	N	PFS (months)	95% CI
< 1.5	22	9.1	3.7–14.5
≥1.5	25	7.6	6.7–8.5

P=0.69

b

BMI	N	PFS (months)	95% CI
< 21.5	23	7.6	2.0–13.2
≥ 21.5	24	7.6	6.6–8.6

P=0.38
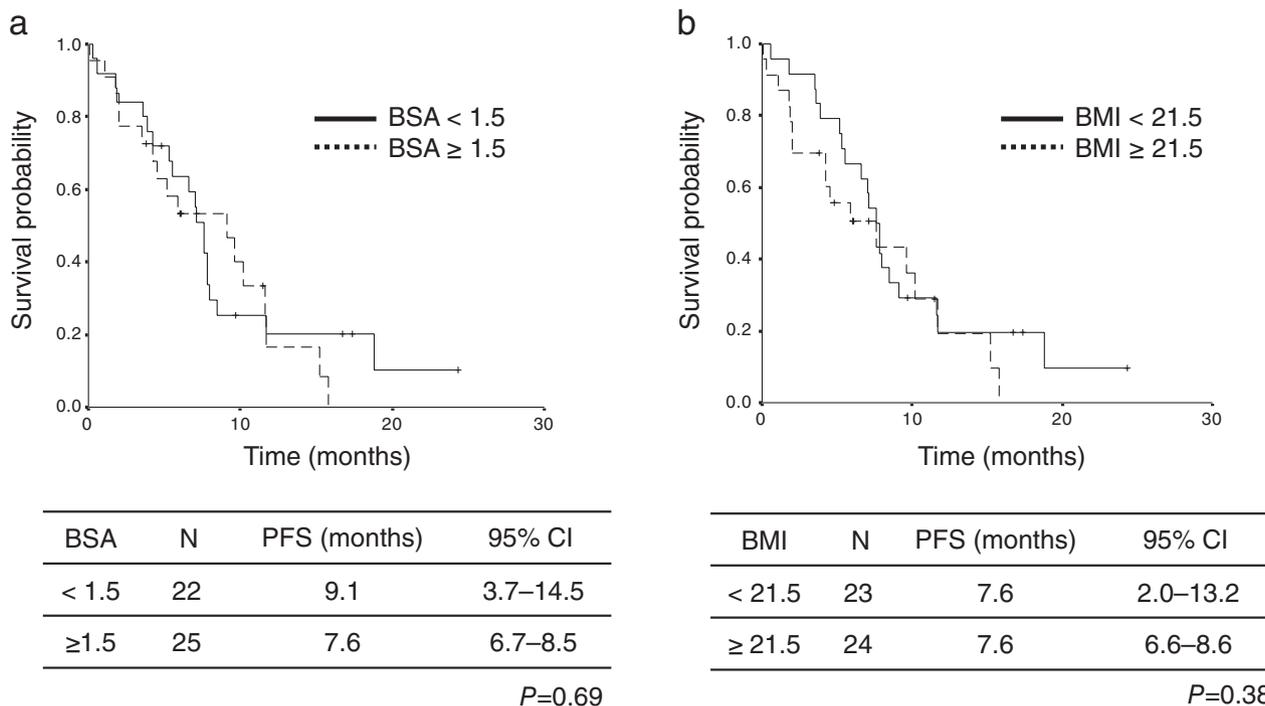
Figure 2 Kaplan–Meier plots of progression free survival (PFS) in relation to body size: (**a**) body surface area (BSA) (——) BSA < 1.5, and (·········) BSA ≥ 1.5; and (**b**) body mass index (BMI) (——) BMI < 21.5, and (·········) BMI ≥ 21.5. CI, confidence interval.

BSA or BMI. In addition, we also changed the cutoff values of BSA and BMI but failed to detect any statistically significant differences in PFS.

A previous phase III (AURA III study) showed an ORR to osimertinib of 71% (95% CI 65–76) in patients with T790M-positive advanced NSCLC who experienced disease

Table 7 Cox regression analysis of PFS

PFS	Univariate analysis		Multivariate analysis	
Variable	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Gender Male vs. Female	0.95 (0.47–1.88)	0.87		
Age (years), median, range < 75 vs. ≥ 75	0.59 (0.29–1.17)	0.13	0.33 (0.15–0.72)	0.005
Performance status 0–1 vs. 2–3	2.09 (1.01–4.30)	0.046	2.49 (1.14–5.43)	0.022
EGFR genotype Exon 19 deletion L858R point mutation	1.88 (0.95–3.72)	0.07	2.83 (1.32–6.06)	0.007
Smoking status Current smoker Never or former light smoker	1.24 (0.62–2.48)	0.54		
Stage Postoperative recurrence Stage IV	1.66 (0.64–4.33)	0.30		
Brain metastasis Positive vs. Negative	2.06 (1.05–4.05)	0.036	Excluded	
Number of prior regimens 0 vs. ≥ 1	2.03 (1.03–4.00)	0.041	Excluded	
BSA < 1.51 vs. ≥ 1.51	0.88 (0.45–1.70)	0.70		
BMI < 21.5 vs. ≥ 21.5	0.75 (0.39–1.45)	0.39		

BMI, body mass index; BSA, body surface area; CI, confidence interval; PFS, progression-free survival.
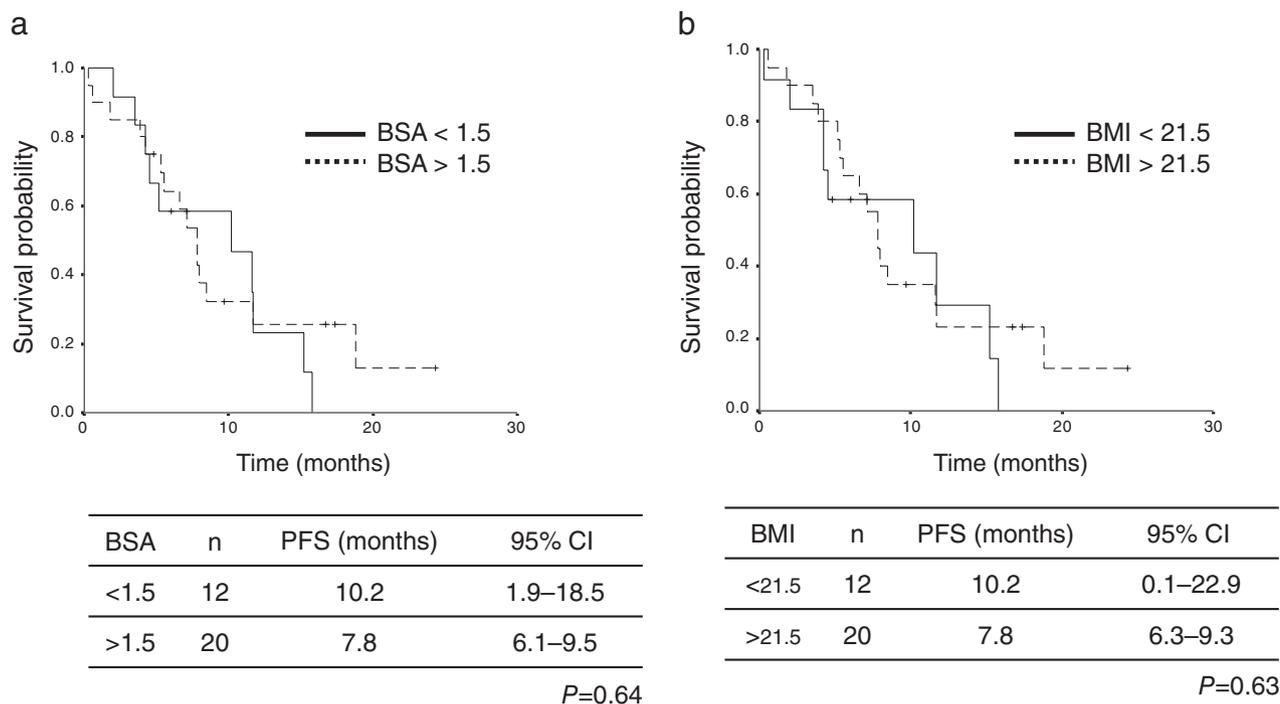
Figure 3 Kaplan–Meier plots of progression free survival (PFS) in relation to body size of patients with good performance status: (**a**) body surface area (BSA) (———) BSA < 1.5, and (··········) BSA ≥ 1.5; and (**b**) body mass index (BMI) (———) BMI < 21.5, and (··········) BMI ≥ 21.5. CI, confidence interval.

progression after first-line *EGFR*-TKI therapy,[22] which is higher than the 57.4% ORR observed in our study. The number of patients in our study with poor PS and the number of chemotherapy regimens prior to osimertinib therapy per patient were 16 (34%) and 2, respectively. However, in the AURA III study, all patients had good PS and 96% had received only one prior regimen, explaining the differences in ORR and PFS of osimertinib therapy between our study and the AURA III trial.

We previously found that the efficacy of gefitinib in patients with NSCLC harboring an *EGFR* mutation did not differ in relation to their BSA.[24] Similarly, Imai *et al.* reported that gefitinib efficacy in patients with NSCLC harboring sensitive *EGFR* mutations did not differ relative to BSA, body weight, and BMI.[25] Another study showed that the efficacy of gefitinib in NSCLC patients did not significantly differ between doses of 250 or 500 mg/day.[26,27] According to results of these studies, although most cytotoxic anticancer agent regimens are based on BSA-adjusted doses, we conclude that the dosage of gefitinib could not be adjusted based on a body size variable, such as BSA. Furthermore, a Phase I/II AURA trial was conducted to determine the safety and efficacy of osimertinib in patients with advanced NSCLC who experienced disease progression after previous treatment with *EGFR*-TKIs.[21] Among the patients with the T790M mutation, osimertinib had

ORRs of 83%, 79%, and 77% at daily doses of 80, 160, and 240 mg, respectively. Thus, it is reasonable to conclude that the tumor responses of osimertinib therapy were not dose-dependent, and the observations of our study appear to support the lack of a correlation between tumor response and osimertinib dose.

There were several limitations to our study. Firstly, the sample size may not have been sufficient. Secondly, there was no pharmacokinetic validation accompanying the observations on the efficacy of osimertinib in relation to BSA and BMI.

In conclusion, the efficacy of osimertinib in patients with T790M-positive advanced NSCLC who experienced disease progression after prior *EGFR*-TKI therapy did not significantly vary relative to BSA or BMI. Based on our findings, we propose that the next step in the development of effective osimertinib regimens could be a study examining the relationship between body size variables and the efficacy of osimertinib monotherapy in the first-line setting for NSCLC patients with sensitive *EGFR* mutations.

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Disclosure

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