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Real-world practice patterns for patients with advanced non-small cell lung cancer: multicenter retrospective cohort study in Japan

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Background: Recommended therapies for advanced/metastatic non-small cell lung cancer (NSCLC) have changed with the advent of targeted therapies. The objectives of this retrospective chart review study were to describe treatment patterns, biomarker testing practices, and health care resource use for advanced NSCLC at 5 sites in Japan.

Patients and methods: We studied anonymized medical record data of patients aged ≥18 years who initiated systemic therapy for newly diagnosed stage IIIB or IV NSCLC from January 2011 through June 2013. Data were analyzed descriptively by histology and mutation status. Overall survival was estimated using the Kaplan–Meier method.

Results: We studied 175 patients, including 43 (25%), 129 (74%), and 3 (2%) with squamous, nonsquamous, and unknown NSCLC histology, respectively; 83% had stage IV NSCLC. Overall, 123 patients (70%) were male; the median age was 70 years (range, 47–86); and 33 (19%) were never-smokers. In the nonsquamous cohort, 105 (81%) and 25 (19%) of patients were tested for epidermal growth factor receptor (*EGFR*) mutation and anaplastic lymphoma kinase (*ALK*) rearrangement, respectively; 44 (42%) had *EGFR*-positive NSCLC and 2 (8%) had *ALK*-positive NSCLC, including 26/46 (57%) women and 21/46 (46%) never-smokers. In the squamous cohort, 17 (40%) and 4 (9%), respectively, were tested; 1 *EGFR*-positive tumor was detected. After first-line therapy, 105 (60%) patients received second-line, and 54/105 (51%; or 31% overall) received third-line therapy. *EGFR* tyrosine kinase inhibitors were most commonly prescribed for *EGFR*-positive NSCLC across all lines. In the nonsquamous *EGFR*/*ALK*-negative/unknown cohort, most received first-line platinum combinations, particularly younger patients (78% ≥75 years vs 93% <75 years old). The average hospitalization was 21 days/admission. The median (95% CI) overall survival from start of first-line therapy was 9.9 months (7.6–11.7) for all patients and 17.9 months (9.9–24.4) for patients with *EGFR*/*ALK*-positive status.

Conclusion: Biomarker testing is common for nonsquamous NSCLC at the 5 Japanese study sites. Treatment is personalized by mutation status and age, per guideline recommendations.

Keywords: predictive biomarker, health care resource use, Japan, non-small cell lung cancer, systemic therapy, treatment patterns

Introduction

In Japan, cancer has been the leading cause of death since 1981.[1] In 2015, lung cancer was responsible for over 75,000 deaths, representing ~20% of all cancer-related deaths and the number 1 and 2 cause of cancer-related deaths in men and women, respectively.[1–4] Over 100,000 new cases of lung cancer are diagnosed annually in Japan, the majority of which (74%) are diagnosed at advanced stages of disease with poor prognosis.[1]

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The Japanese guidelines for treatment of lung cancer recommend that therapy be based on histology, mutation status, and age (<75 vs ≥75 years old).[5] For patients with advanced nonsquamous non-small cell lung cancer (NSCLC) harboring a sensitizing mutation in the epidermal growth factor receptor (*EGFR*) gene or an anaplastic lymphoma kinase (*ALK*) rearrangement, the guidelines recommend monotherapy with the appropriate *EGFR* or *ALK* tyrosine kinase inhibitor (TKI) or a platinum combination with or without bevacizumab. The prevalence of *EGFR* mutations in NSCLC is higher in Asian than Caucasian patient populations.[6–9] The reported prevalence of *EGFR* mutations in Japanese and East Asian patients with NSCLC is ~40%,[6,9] with up to 59% of moderately to well-differentiated adenocarcinomas carrying the mutation.[9,10] The *EGFR* mutation is more common in women and nonsmokers.[9,11] The prevalence of *ALK*-rearranged (*ALK*-positive) NSCLC is lower, from 4% to 7% by different estimates;[12,13] and *ALK*-positive tumors are more common in younger patients, light or nonsmokers, with adenocarcinoma.[12,14] These 2 mutations are usually, but not always, mutually exclusive.[7]

As the understanding of tumor biology has evolved rapidly in recent years, an understanding of real-world treatment practices is important to benchmark changes in treatment recommendations. Japan was 1 of 9 countries participating in a global study of real-world treatment patterns for advanced NSCLC (also including Australia, Brazil, Canada, Germany, Italy, Korea, Spain, and Taiwan).[32] The primary objectives of this multinational, observational study were to describe the treatment patterns, biopsy and biomarker testing practices, and health care resource use (HCRU) for patients who initiated first-line systemic therapy for newly diagnosed stage IIIB or IV NSCLC from January 2011 to July 2013. Here, we report the findings for the Japanese cohort.

Methods

Study design and patients

This retrospective chart review study was conducted at 5 sites in Japan; these sites were selected based on positive responses to a site qualification questionnaire indicating an interest in study participation, experience in managing patients with NSCLC, availability of biomarker testing data, and adequate resources to support participation. Both academic and community oncology centers were considered, with the goal of including from 150 to 200 patients. The 5 study sites included 1 academic center (Yachiyo Medical Center at Tokyo Women's University), a private hospital (Tsuboi Cancer Center Hospital), a public cancer center (Gunma Prefectural Cancer Center), a general hospital (KKR Sapporo Medical Center), and a specialized hospital (Kanagawa Cardiovascular and Respiratory Center).

The study eligibility period was January 1, 2011, to July 1, 2013. Patients 18 years and older who initiated first-line systemic therapy for newly diagnosed stage IIIB or IV NSCLC during this 2.5-year period were eligible for the study. The date of initiation of first-line therapy for each patient was defined as their index date. Eligible patients were identified by retrospective chart review starting at the end of the eligibility period and working backward in time. Patient follow-up concluded on August 10, 2015, and eligible patients had to have complete medical records until that date (or death, if earlier), thereby ensuring a minimum potential follow-up of over 2 years for each patient.

We required histologic or cytologic confirmation of stage IIIB/IV NSCLC. In the study protocol, investigators were provided with NSCLC staging guidelines according to the TNM classification of the Union for International Cancer Control and the American Joint Committee on Cancer.[15,16] Patients who did not initiate systemic therapy for NSCLC were excluded, as were patients enrolled in an interventional clinical trial or other clinical study, those with a concomitant or prior history of other malignancy, and those with an initial diagnosis of an earlier stage of NSCLC (stage I–IIIA) that had progressed to stage IIIB or IV.

The study protocol conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013) and was approved by the head of each study site after review by the institutional ethics committee, reported in the Supplementary materials section. Informed consent requirements were waived by the ethics committees in accordance with Japanese clinical study guidelines for noninterventional research involving pre-existing data.[17]

Data collection

Electronic case report forms (eCRFs) were used to collect anonymized demographic and clinical data from patient charts by trained chart abstractors at each study site. Each patient was given a unique number as an identifier on the eCRFs. Diagnosis-, biomarker-, and treatment-related data were collected from the index date (i.e., start of first-line therapy) for each patient, including type of biomarker tests, testing dates and results, dose and duration of administered therapies, number of clinic and any emergency visits, and number and duration of hospitalizations.

The Eastern Cooperative Oncology Group (ECOG)[18] or Karnofsky scale[19] was used to assess performance status

on the index date. Maintenance therapy was defined as any therapy given to a patient after first-line induction but before the start of second-line therapy. The duration of each treatment line was calculated (in days as the stop date of treatment line – start date of treatment line +1 day). The primary site investigator confirmed all data entry and provided any assessments that required a medical professional opinion, such as identifying the date of progression after treatment and deciding whether a dose delay, omission of a dose, or utilization of a health care resource occurred secondary to a treatment-related adverse event.

Statistical analyses

We performed descriptive analyses of demographic, diagnostic, treatment-related, and HCRU data. Results were reported using summary statistics, including frequency count and percentage for categorical variables, and patient number, mean, SD, median, and range for continuous and count variables. The proportion of missing data was reported for key variables; missing data were not imputed.

Treatment patterns were evaluated by line of therapy and histology, *EGFR*-mutation and *ALK*-rearrangement status, and age group (<75 years vs ≥75 years old). We categorized treatment regimens into 4 major categories: platinum-based combination, nonplatinum combination, single agent, and targeted therapy (i.e., *EGFR*/*ALK* TKI). Overall survival (OS) was estimated using the Kaplan–Meier product-limit method.

This was an observational study with no a priori hypothesis testing; therefore, we did not undertake a formal calculation of sample size and statistical power.

Analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

Five sites in Japan enrolled a total of 175 patients, including 43 (25%), 129 (74%), and 3 (2%) with squamous, nonsquamous, and unknown NSCLC histology, respectively. Index dates ranged from January 24, 2011 to June 27, 2013.

Overall, 123 (70%) patients were male; the median age was 70 years and age range, from 47 to 86 years. Approximately one-third of patients were 75 years or older (Table 1). In the squamous cohort, the proportion of

Table 1 Demographic and clinical characteristics of patients with advanced NSCLC by mutation status and histology

Characteristic	Histology			All patients[b]
	Squamous[a]	Nonsquamous (n=129)		
	(n=43)	*EGFR*/*ALK* positive (n=46)	*EGFR*/*ALK* negative or unknown (n=83)	(N=175)
Sex, male, n (%)	37 (86)	20 (44)	64 (77)	123 (70)
Age at index date (years)				
Median (range)	70 (57–86)	71 (51–86)	67 (47–81)	70 (47–86)
<75 years, n (%)	29 (67)	32 (70)	60 (72)	123 (70)
≥75 years, n (%)	14 (33)	14 (30)	23 (28)	52 (30)
History of smoking, n (% of nonmissing)				
Current smoker	7 (16)	0	14 (17)	21 (12)
Former smoker	35 (81)	25 (54)	59 (71)	120 (69)
Never smoker	1 (2)	21 (46)	9 (11)	33 (19)
Missing, n	0	0	1	1
Height, mean (SD), m	1.60 (0.07)	1.57 (0.08)	1.63 (0.08)	1.60 (0.08)
Weight, mean (SD), kg[c]	59.5 (9.1)	56.5 (8.8)	59.6 (9.6)	58.7 (9.3)
Comorbidity, n (%)				
Hypertension, medically treated	20 (48)	16 (35)	25 (30)	62 (37)
Diabetes mellitus	3 (7)	3 (7)	19 (23)	26 (15)
COPD	4 (9)	0	14 (17)	18 (10)
Cardiovascular disease	2 (5)	0	11 (13)	13 (7)
Cerebrovascular disease	2 (5)	2 (4)	4 (5)	8 (5)
Other	24 (56)	31 (67)	38 (46)	95 (54)

Notes: Some percentages may not total 100 because of rounding. [a]One female never-smoker, age 66 years, stage IV NSCLC diagnosed with biopsy sample, ECOG PS of 2, and lymph node metastasis with positive *EGFR* mutation status was included in the squamous cohort and received radiotherapy before the index date and subsequently first-, second-, and third-line therapy. [b]All patients column includes 3 patients with unknown histology NSCLC. [c]Weight data were missing for 8, 8, 7, and 25 patients in squamous, nonsquamous *EGFR*/*ALK*-positive, nonsquamous *EGFR*/*ALK*-negative, and the full patient cohorts, respectively.

Abbreviations: *ALK*, anaplastic lymphoma kinase; COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

male patients was higher than in the nonsquamous cohort (86% vs 65% male), as was the proportion of current and former smokers (98% vs 76% in the nonsquamous cohort). NSCLC was at stage IV upon diagnosis for most patients overall (83%), and for 70% of those in the squamous cohort (Table 2). Lymph nodes, lung (other than the primary site), and bone were the most common sites of metastases. The majority of patients (84%) had an ECOG performance status of 0 or 1 (Table 2).

Patient demographic and clinical characteristics are reported in Tables 1 and 2 according to *EGFR* mutation and *ALK* rearrangement status. In the nonsquamous cohort, patients with positive *EGFR* or *ALK* mutation status, compared with patients with negative or unknown results, were more likely to be female (57% vs 23%) and more likely to be never-smokers (46% vs 11%).

Biopsy and biomarker testing patterns

The diagnosis of NSCLC was made by tissue biopsy for most patients, including 66% solely with biopsy and 14% with biopsy and cytology (Table 2). Overall, the majority of patients (91%) had at least 1 biopsy during the study (Table 3).

Three-quarters of patients overall (n=130; 74%) had at least 1 biomarker test performed, including 17 (40%), and 110 (85%) of those in squamous and nonsquamous cohorts, respectively, and all 3 patients in the unknown histology cohort (Table 3). Overall, 125 (71%) and 30 (17%) patients were tested for *EGFR* mutation and *ALK* rearrangement, respectively. The biomarker test results are reported in Table 3.

Treatment patterns

As per eligibility criteria, all 175 patients received first-line therapy. A total of 105 (60%) patients continued to

Table 2 Lung cancer-related characteristics of patients with advanced NSCLC by mutation status and histology

Characteristic	Histology			All patients[b]
	Squamous[a]	Nonsquamous (n=129)		
	(n=43)	*EGFR*/*ALK* positive (n=46)	*EGFR*/*ALK* negative or unknown (n=83)	(N=175)
Basis of diagnosis, n (%)				
Tissue biopsy only	31 (72)	24 (52)	61 (73)	116 (66)
Cytology only	5 (12)	14 (30)	14 (17)	35 (20)
Tissue biopsy and cytology	7 (16)	8 (17)	8 (10)	24 (14)
Stage at diagnosis, n (%)				
Stage IIIB	13 (30)	3 (7)	13 (16)	29 (17)
Stage IV	30 (70)	43 (93)	70 (84)	146 (83)
Most common locations of metastases at index, n (%)				
Lymph nodes	21 (49)	15 (33)	43 (52)	80 (46)
Lung (other than primary)	17 (40)	12 (26)	20 (24)	50 (29)
Bone	4 (9)	22 (48)	28 (34)	57 (33)
Brain	5 (12)	15 (33)	15 (18)	36 (21)
Liver	2 (5)	5 (11)	11 (13)	19 (11)
ECOG PS at index date, n (% of nonmissing)				
0	11 (41)	11 (41)	25 (47)	47 (44)
1	12 (44)	11 (41)	20 (38)	44 (41)
2	3 (11)	2 (7)	5 (9)	10 (9)
3	1 (4)	3 (11)	3 (6)	7 (6)
Missing, n	16	19	30	67
Systemic therapy, n (%)				
First-line therapy	43 (100)	46 (100)	83 (100)	175 (100)
Second-line therapy	30 (70)	30 (65)	43 (52)	105 (60)
Third-line therapy	15 (35)	15 (33)	22 (27)	54 (31)
Treatment prior to index date, n (%)				
Surgery only	3 (7)	3 (7)	6 (7)	12 (7)
Radiotherapy only	9 (21)	3 (7)	14 (17)	26 (15)
Surgery + radiotherapy	1 (2)	0	0	1 (1)

Notes: Some percentages may not total 100 because of rounding. [a]One female never-smoker, age 66 years, stage IV NSCLC diagnosed with biopsy sample, ECOG PS of 2, and lymph node metastasis with positive *EGFR* mutation status was included in the squamous cohort and received radiotherapy before the index date and subsequently first-, second-, and third-line therapy. [b]All patients column includes 3 patients with unknown histology NSCLC.

Abbreviations: *ALK*, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

Table 3 Biomarker and biopsy practice patterns by histology for patients with advanced NSCLC

	Squamous (n=43)	Nonsquamous (n=129)	Unknown (n=3)	All patients (N=175)
Total patients with biopsy	41 (95)	115 (89)	3 (100)	159 (91)
Mean (SD) number of biopsies per patient	1.0 (0.2)	1.1 (0.5)	1.3 (0.6)	1.1 (0.4)
Patients with re-biopsy	1 (2)	5 (4)	1 (33)	7 (4)
At least 1 biomarker test performed	17 (40)	110 (85)	3 (100)	130 (74)
Type of test				
EGFR, n (% of all patients)	17 (40)	105 (81)	3 (100)	125 (71)
ALK, n (% of all patients)	4 (9)	25 (19)	1 (33)	30 (17)
KRAS, n (% of all patients)	0	1 (1)	0	1 (1)
EGFR test result, n (% of patients tested)				
Positive *EGFR* mutation status	1 (6)	44 (42)	2 (67)	47 (38)
Negative *EGFR* mutation status	16 (94)	60 (57)[a]	1 (33)	77 (62)[a]
ALK test result, n (% of patients tested)				
Positive for *ALK* rearrangement	0	2 (8)	0	2 (7)
Negative for *ALK* rearrangement	4 (100)	23 (92)	1 (100)	28 (93)
Timing of biomarker testing, n	16	109	3	128
Before confirmed diagnosis[b]	9 (56)	68 (62)	1 (33)	78 (61)
Before start of 1L therapy, after diagnosis	6 (38)	40 (37)	2 (67)	48 (38)
Before start of 2L therapy, after 1L therapy	1 (6)	4 (4)	0	5 (4)
Before start of 3L therapy, after 2L therapy	1 (6)	4 (4)	0	5 (4)
After 3L therapy	0	1 (1)	0	1 (1)
Missing, n	1	1	0	2

Notes: Data are n (%) unless otherwise noted. [a]*EGFR*-mutation test results for 1 patient were unknown/inconclusive. [b]Diagnosis made by tissue biopsy and/or cytology.
Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

second-line therapy, including 30/43 (70%) with squamous NSCLC, 30/46 (65%) with *EGFR*/*ALK*-positive nonsquamous NSCLC, and 43/83 (52%) with *EGFR*/*ALK*-negative or -unknown nonsquamous NSCLC (Table 4). Of the patients who received second-line therapy, 54/105 (51%; or 31% overall) received third-line therapy. Two of the 3 patients with unknown histology received second- and third-line therapy.

The most common first-, second-, and third-line therapies administered to patients in the study are summarized in Table 4 by regimen category for all patients and according to histology, *EGFR*/*ALK* mutation status for the nonsquamous cohort, and age group. (More detail on specific regimens is provided in Tables S1–S4).

For first-line therapy, two-thirds of patients (66%), including 84% and 60% of patients in squamous and nonsquamous histology cohorts, respectively, received a platinum-based combination, most commonly carboplatin–paclitaxel. One-quarter (25%) of patients, including all but 1 with positive *EGFR* or *ALK* mutation status, received an *EGFR*/*ALK* TKI as first-line therapy (Table 4; Table S3). For second-line therapy, the majority of the 105 patients (47%) received a single agent, most commonly docetaxel in the squamous cohort (47%) and pemetrexed (22%) or docetaxel (21%) in the nonsquamous cohort. There was no consistent pattern of therapy for the 54 patients who continued to third-line therapy. Single agents were commonly administered (44% overall), including 6 different agents in the squamous cohort and docetaxel (16%) and pemetrexed (11%) in the nonsquamous cohort, while 24% of patients received erlotinib, and 22% received a platinum combination, most of them <75 years old in the nonsquamous cohort (Table 4; Tables S1–S4).

In the nonsquamous cohort, 39 of 44 (89%) patients with *EGFR*-positive status received an *EGFR* TKI in first-line therapy; all but 1 received gefitinib (38/39; 97%). The 2 patients with *ALK*-positive status received crizotinib as first-line therapy; neither one continued therapy beyond first-line. Half or more of patients with *EGFR*-positive status were prescribed an *EGFR* TKI for second-line therapy (15/30; 50%), most commonly erlotinib (11/15; 73%), and for third-line therapy (9/15; 60%), all erlotinib (Table 4; Table S3). By contrast, the patients with negative, unknown, or untested mutation status most commonly received a platinum combination (89%) as first-line and single agents as second-line (67%) and third-line (50%), while patients ≥75 years old received fewer platinum combinations and more single agents than younger patients (Table 4; Table S2). Six percent of patients, overall, received maintenance therapy after first-line (data not shown).

The median (range) durations of treatment for patients with *EGFR*/*ALK*-positive mutation status were 181 (4–1166),

Table 4 Treatment patterns for advanced NSCLC by histology, mutation status, and age group (<75 years vs ≥75 years old)

Treatment regimen[a]	Squamous (n=43)		Nonsquamous (n=129)				All patients (N=175)[b]		All[b] (N=175)
			<75 years (n=92)		≥75 years (n=37)				
	<75 years (n=29)	≥75 years (n=14)	*EGFR/ALK*-positive (n=32)	*EGFR/ALK*-neg/unk (n=60)	*EGFR/ALK*-positive (n=14)	*EGFR/ALK*-neg/unk (n=23)	<75 years (n=123)	≥75 years (n=52)	
First-line therapy									
Platinum-based combination	29 (100)	7 (50)	3 (9)	56 (93)	1 (7)	18 (78)	89 (72)	26 (50)	115 (66)
Platinum, no bevacizumab	29 (100)	7 (50)	2 (6)	50 (83)	1 (7)	13 (57)	82 (67)	21 (40)	103 (59)
Platinum with bevacizumab	0	0	1 (3)	6 (10)	0	5 (22)	7 (6)	5 (10)	12 (7)
Single agent	0	6 (43)	1 (3)	4 (7)	0	5 (22)	5 (4)	11 (21)	16 (9)
Docetaxel	0	5 (36)	0	2 (3)	0	1 (4)	2 (2)	6 (12)	8 (5)
Carboplatin	0	1 (7)	0	1 (2)	0	0	1 (1)	1 (2)	2 (1)
Paclitaxel	0	0	0	0	0	2 (9)	0	2 (4)	2 (1)
Tegafur/gimeracil/oteracilc	0	0	0	1 (2)	0	1 (4)	1 (1)	1 (2)	2 (1)
Bevacizumab	0	0	1 (3)	0	0	0	1 (1)	0	1 (1)
Pemetrexed	0	0	0	0	0	1 (4)	0	1 (2)	1 (1)
EGFR/ALK TKI	0	1 (7)	28 (88)	0	13 (93)	0	29 (24)	15 (29)	44 (25)
Gefitinib	0	0	25 (78)	0	13 (93)	0	26 (21.1)	14 (27)	40 (23)
Erlotinib	0	1 (7)	1 (3)	0	0	0	1 (1)	1 (2)	2 (1)
Crizotinib	0	0	2 (6)	0	0	0	2 (2)	0	2 (11)
Second-line therapy	n=22	n=8	n=21	n=32	n=9	n=11	n=77	n=28	N=105
Platinum-based combination	8 (36)	0	11 (52)	8 (25)	2 (22)	1 (9)	27 (35)	3 (11)	30 (29)
Platinum, no bevacizumab	8 (36)	0	7 (33)	5 (16)	1 (11)	1 (9)	20 (26)	2 (7)	22 (21)
Platinum with bevacizumab	0	0	4 (19)	3 (9)	1 (11)	0	7 (9)	1 (4)	8 (8)
Nonplatinum combination	0	0	0	2 (6)	0	0	2 (3)	0	2 (2)
Nonplatinum, no bevacizumab	0	0	0	1 (3)	0	0	1 (1)	0	1 (1)
Nonplatinum with bevacizumab	0	0	0	1 (3)	0	0	1 (1)	0	1 (1)
Single agent	12 (55)	8 (100)	1 (5)	21 (66)	1 (11)	8 (73)	34 (44)	17 (61)	51 (49)
Docetaxel	10 (46)	4 (50)	0	12 (38)	0	3 (27)	22 (29)	7 (25)	29 (28)
Pemetrexed	1 (5)	0	1 (5)	9 (28)	1 (11)	5 (45)	11 (14)	6 (21)	17 (16)
Gemcitabine	0	3 (38)	0	0	0	0	0	3 (11)	3 (3)
Tegafur/gimeracil/oteracilc	1 (5)	1 (13)	0	0	0	0	1 (1)	1 (4)	2 (2)
EGFR/ALK TKI	2 (9)	0	9 (43)	1 (3)	6 (67)	2 (18)	14 (18)	8 (29)	22 (21)
Erlotinib	2 (9)	0	6 (29)	1 (3)	5 (56)	2 (18)	10 (13)	7 (25)	17 (16)
Gefitinib	0	0	1 (5)	0	1 (11)	0	1 (1)	1 (4)	2 (2)
Afatinib	0	0	2 (10)	0	0	0	2 (3)	0	2 (2)
Crizotinib	0	0	0	0	0	0	1 (1)	0	1 (1)
Third-line therapy	n=12	n=3	n=11	n=17	n=4	n=5	n=42	n=12	N=54
Platinum-based combination	1 (8)	0	3 (27)	6 (35)	0	1 (20)	11 (26)	1 (8)	12 (22)
Platinum, no bevacizumab	1 (8)	0	3 (27)	5 (29)	0	1 (20)	10 (24)	1 (8)	11 (20)
Platinum with bevacizumab	0	0	0	1 (6)	0	0	1 (2)	0	1 (2)
Nonplatinum combination	2 (17)	0	2 (18)	1 (6)	0	0	5 (12)	0	5 (9)
Nonplatinum, no bevacizumab	2 (17)	0	2 (18)	1 (6)	0	0	5 (12)	0	5 (9)
Single agent	8 (67)	3 (100)	1 (9)	8 (47)	0	3 (60)	18 (43)	6 (50)	24 (44)
Docetaxel	1 (8)	0	1 (9)	4 (24)	0	1 (20)	7 (17)	1 (8)	8 (15)
Pemetrexed	1 (8)	1 (33)	0	2 (12)	0	2 (40)	3 (7)	3 (25)	6 (11)
Tegafur/gimeracil/oteracil[c]	3 (25)	2 (67)	0	0	0	0	3 (7)	2 (17)	5 (9)
Gemcitabine	1 (8)	0	0	1 (6)	0	0	2 (5)	0	2 (4)

(*Continued*)

Table 4 (*Continued*)

Treatment regimen[a]	Squamous (n=43)		Nonsquamous (n=129)				All patients (N=175)[b]		All[b] (N=175)
			<75 years (n=92)		≥75 years (n=37)				
	<75 years (n=29)	≥75 years (n=14)	*EGFR*/*ALK*-positive (n=32)	*EGFR*/*ALK*-neg/unk (n=60)	*EGFR*/*ALK*-positive (n=14)	*EGFR*/*ALK*-neg/unk (n=23)	<75 years (n=123)	≥75 years (n=52)	
Paclitaxel	1 (8)	0	0	0	0	0	1 (2)	0	1 (2)
Vinorelbine	1 (8)	0	0	0	0	0	1 (2)	0	1 (2)
Amrubicin HCl	0	0	0	1 (6)	0	0	1 (2)	0	1 (2)
EGFR/*ALK* TKI	1 (8)	0	5 (45)	2 (12)	4 (100)	1 (20)	8 (19)	5 (42)	13 (24)
Erlotinib	1 (8)	0	5 (45)	2 (12)	4 (100)	1 (20)	8 (19)	5 (42)	13 (24)

Notes: Data are n (%). Some percentages may not total 100 because of rounding. [a]The treatment regimens were defined as follows: Platinum-based combination was defined as a regimen with 2 or more anticancer therapies including carboplatin or cisplatin. Nonplatinum combination was defined as a regimen with 2 or more anticancer therapies not including carboplatin, cisplatin, or targeted therapy (*EGFR* TKI or *ALK* inhibitor). Single agent was defined as a regimen of 1 anticancer drug that was not an *EGFR*/*ALK* TKI. Targeted therapy included *EGFR* TKIs (erlotinib, gefitinib, afatinib) and *ALK* inhibitors (crizotinib). [b]All patients column includes 3 patients in first-line and 2 patients in second- and third-line with unknown histology NSCLC. [c]Oral anticancer drug composed of tegafur, gimeracil, and oteracil potassium at a molar ratio of 1:1:0.4.

Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; neg, negative; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; unk, unknown.

34 (1–606), and 19 (1–211) days for first-, second-, and third-line therapy, respectively; and the corresponding durations for those with *EGFR*-negative or unknown mutation status were 68 (1–451), 28 (1–985), 43 (1–394) days, respectively.

Overall survival

The median OS for the full population was 9.9 months (95% CI, 7.6–11.7) from the start of first-line therapy and 4.7 months (95% CI, 3.8–5.8) from the start of second-line therapy.

For the squamous cohort, median OS was 10.1 months (95% CI, 7.3–14.4) and 5.6 months (95% CI, 3.1–9.4) from the start of first- and second-line therapy, respectively. As depicted in the Kaplan–Meier plots (Figures 1 and 2), the survival curves for the nonsquamous *EGFR*/*ALK*-positive and *EGFR*/*ALK*–negative cohorts separated distinctly between 5 and 30 months after initiation of first-line therapy, while the curves after second-line therapy were similar. The median OS for patients with *EGFR*/*ALK*-negative or unknown status was 6.9 months (95% CI, 5.6–10.0) and 4.0 months (95% CI, 2.8–4.8) from the start of first- and second-line therapy, respectively, while that for patients with *EGFR*/*ALK*-positive status was 17.9 months (95% CI, 9.9–24.4) and 4.0 months (3.3–12.0), respectively.

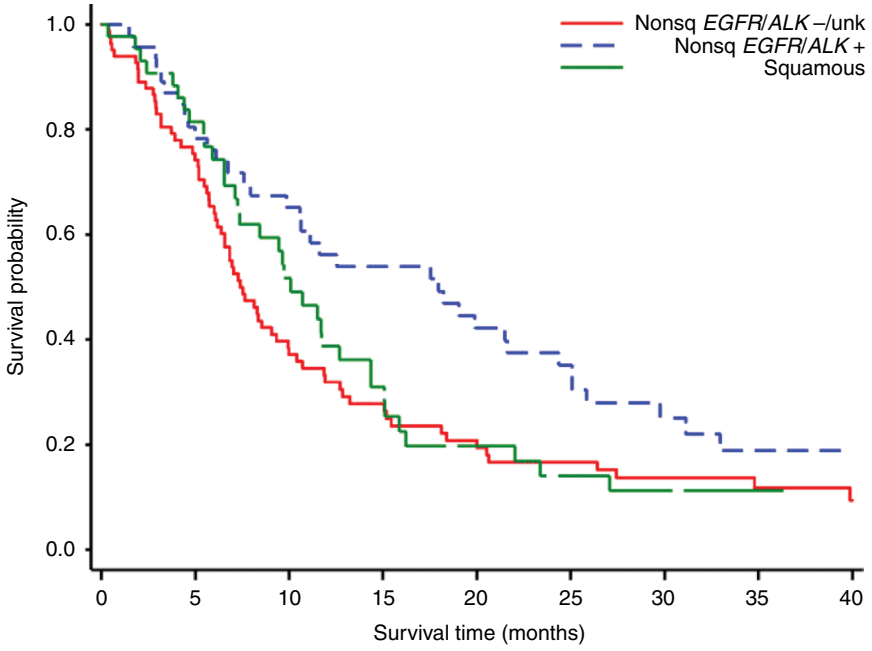
Health care resource use

The numbers of hospital inpatient admissions and inpatient visits without overnight stay per 100 patient-weeks were similar during first- and second-line therapy, as summarized in Table 5: namely, 5.5 vs 5.1 inpatient admissions and 37.7 vs 38.2 inpatient visits without overnight stay, respectively. The number of emergency department visits was relatively low but doubled with increasing line of therapy from 0.2 to 0.4 emergency department visits per 100 patient-weeks. Similarly, the overall average length of hospitalization increased from 19.1 days in first-line to 21.7 days in second-line therapy. The average length of hospitalization was longest for the *EGFR*/*ALK*-positive nonsquamous cohort in first-line (23.7 days) and for the squamous cohort in second-line (26.0 days), although both of these cohorts had the fewest hospital admissions per 100 patient-weeks (Table 5). The average hospital stay overall was 21 days/admission. The total number of image tests was greatest in first-line, although the number per 100 patient-weeks was similar in the 2 lines of therapy.

Discussion

This retrospective observational study has given us the opportunity to evaluate real-world clinical management of patients who initiated systemic therapy for advanced NSCLC at 5 sites in Japan from 2011 to 2013. We found that the proportions of patients with nonsquamous NSCLC tested for *EGFR* mutation and *ALK* rearrangement at these sites were 81% and 19%, respectively, with 42% and 8% *EGFR*- and *ALK*-positive, respectively. In the squamous cohort, the proportions tested were 40% and 9%, respectively, with only 1 *EGFR*-positive tumor detected. The treatment patterns for patients with *EGFR*/*ALK*-positive nonsquamous NSCLC differed substantially from those with mutation-negative (or unknown) nonsquamous NSCLC. The majority of patients with *EGFR*- or *ALK*-positive tumors received an appropriate TKI, suggesting that treatment was personalized according to mutation status.

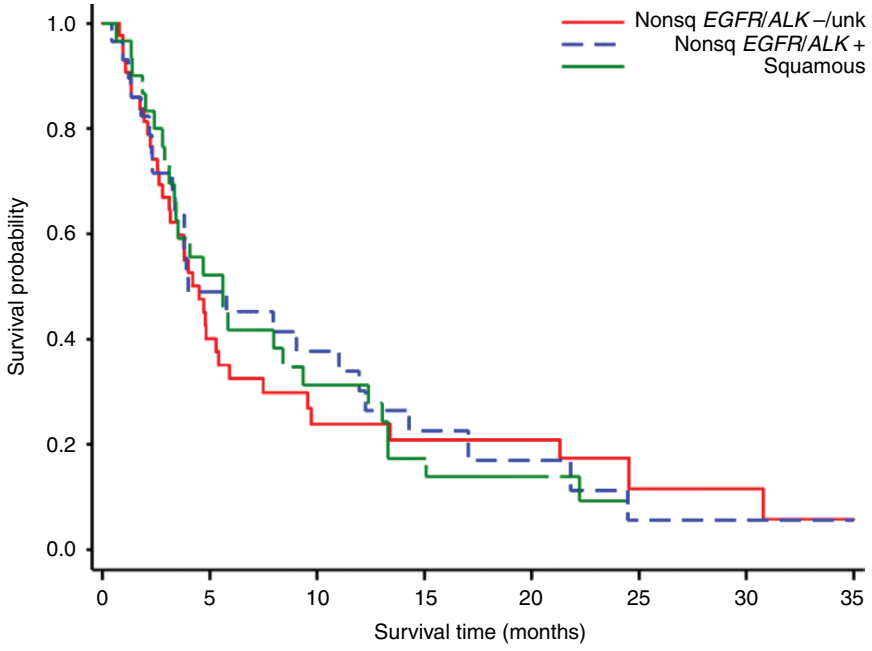
The Japanese lung cancer guidelines recommend that older patients (≥75 years) with nonsquamous *EGFR*-negative



Number of patients at risk									
Nonsq *EGFR*/*ALK* –/unk	82	59	29	20	15	12	9	6	4
Nonsq *EGFR*/*ALK* +	46	36	29	24	18	15	9	5	1
Squamous	43	35	20	11	7	5	3	1	0

Figure 1 Kaplan–Meier plot of overall survival for patients with squamous non-small cell lung cancer (NSCLC) and those with nonsquamous NSCLC, by mutation status from initiation of first-line therapy.

Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *EGFR*/*ALK* +, positive status; Nonsq, nonsquamous; –/unk, negative/unknown status.



Number of patients at risk								
Nonsq *EGFR*/*ALK* –/unk	43	16	8	7	6	2	2	2
Nonsq *EGFR*/*ALK* +	29	13	10	6	3	1	1	1
Squamous	30	15	9	5	3	0		

Figure 2 Kaplan–Meier plot of overall survival for patients with squamous non-small cell lung cancer (NSCLC) and those with nonsquamous NSCLC, by mutation status from initiation of second-line therapy.

Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *EGFR*/*ALK* +, positive status; Nonsq, nonsquamous; -/unk, negative/unknown status.

Table 5 Weekly HCRU by histology and mutation status during first-line or second-line therapy for advanced NSCLC

Weekly HCRU during first-line therapy	**Squamous (n=43)**	**Nonsquamous (n=129)**		**All patients[a] (N=175)**
		***EGFR/ALK* positive (n=46)**	***EGFR/ALK* neg/unk (n=83)**	
Hospital inpatient admissions[b]				
Total no. of inpatient admissions	54	43	143	242
No. of inpatient admissions per 100 pt-wk	6.13	2.36	8.91	5.49
Average LOS per admission, days	19.22	23.70	18.36	19.10
Emergency department visits				
Total no. of emergency department visits	6	1	2	9
No. of emergency department visits per 100 pt-wk	0.68	0.06	0.13	0.20
Inpatient hospitalizations without overnight stay				
Total no. of inpatient visits without overnight stay	433	540	642	1661
No. of inpatient visits without overnight stay per 100 pt-wk	49.11	29.61	39.98	37.65
Infusion center outpatient visits				
Total no. of infusion center outpatient visits	31	0	22	53
No. of infusion center outpatient visits per 100 pt-wk	3.52	0	1.37	1.20
Outpatient clinical visits				
Total no. of outpatient clinical visits	428	540	641	1655
No. of outpatient clinical visits per 100 pt-wk	48.54	29.61	39.92	37.65
Image tests				
Total no. of image tests	632	949	1031	2670
No. of image tests per 100 pt-wk	71.68	52.03	64.20	60.51
Weekly HCRU during second-line therapy	**Squamous (n=30)**	***EGFR/ALK* positive (n=30)**	***EGFR/ALK* negative/unk (n=43)**	**All patients[a] (N=105)**
Hospital inpatient admissions[b]				
Total no. of inpatient admissions	10	25	40	77
No. of inpatient admissions per 100 pt-wk	2.97	5.34	5.85	5.13
Average LOS per admission, days	26.00	20.96	22.55	21.71
Emergency department visits				
Total no. of emergency department visits	0	3	3	6
No. of emergency department visits per 100 pt-wk	0	0.64	0.44	0.40
Inpatient hospitalizations without overnight stay				
Total no. of inpatient visits without overnight stay	250	119	198	574
No. of inpatient visits without overnight stay per 100 pt-wk	74.19	25.40	28.96	38.23
Infusion center outpatient visits				
Total no. of infusion center outpatient visits	9	0	2	11
No. of infusion center outpatient visits per 100 pt-wk	2.67	0	0.29	0.73
Outpatient clinical visits				
Total no. of outpatient clinical visits	250	119	198	574
No. of outpatient clinical visits per 100 pt-wk	74.19	25.40	28.96	38.23
Image tests				
Total no. of image tests	301	249	429	986
No. of image tests per 100 pt-wk	89.32	53.16	62.74	65.68

Notes: [a]All patients column includes 3 patients in first-line and 2 patients in second-line with unknown (unk) histology NSCLC. [b]Hospital inpatient admissions did not include emergency department visits.

Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; HCRU, health care resource use; LOS, length of stay; NSCLC, non-small cell lung cancer; pt-wk, patient-weeks.

advanced NSCLC receive nonplatinum monotherapy or a carboplatin combination.[5] We did indeed find that older patients were less likely to receive a platinum combination and more likely to receive a single agent than younger patients, as recommended.

The *EGFR*-mutation testing rates in our study were higher than those in a prior retrospective study in the Asia-Pacific region, which found that, in 2011, the testing rates for *EGFR* mutation were 65% in Japan, the highest of 11 countries surveyed, and included 69% of adenocarcinomas and 50% of squamous NSCLC.[6] While *EGFR*-mutation testing of squamous NSCLC is not considered necessary by the guidelines because of low levels of positivity, the relatively high testing rates for squamous NSCLC in that study and in ours (40%)

could perhaps be explained by concurrent histopathological and biomarker testing of the same sample. Indeed, only 1 squamous tumor in our study and 3% of squamous tumors in the prior study were *EGFR*-positive.[6]

The Japanese guidelines now recommend that all *EGFR*-negative tumors be tested for *ALK* rearrangements to help clinicians choose the most appropriate therapy for their patients.[5] The low rates of *ALK* testing in our study are likely because testing was relatively new, not available at all hospitals, and not considered reliable during much of the eligibility period (January 2011 through June 2013); moreover, the *ALK* inhibitors crizotinib and alectinib were not launched in Japan until May 2012 and September 2014, respectively.

We found that patients with advanced NSCLC experienced substantial HCRU and lengthy hospitalizations. The long duration of hospitalizations was not unexpected because of the common practice until recently of observing patients in hospital for 4 weeks to manage potential adverse events, because of precautions on the gefitinib label[20] and a publicized death from interstitial pneumonia of a gefitinib-treated patient in the early 2000s. Indeed, patients in the *EGFR*/*ALK*-positive cohort had the lengthiest hospital stays in first-line (but not in second-line).

The median OS outcomes for patients in this study were inferior to those found in Phase III clinical trials.[21,22] Older age and the presence of bone metastases have been identified as negative prognostic factors for lung cancer survival in large population-based studies.[23–25] Our patient population included many older patients (30% were ≥75 years old) as well as patients with bone metastases at the index date (33% of the study population). In addition, 16% of patients had ECOG performance status of 2–3, including 5 of 26 patients, or almost one-fifth of those in the *EGFR*/*ALK*-positive nonsquamous cohort with ECOG data; therefore, it is possible that these real-world patients were sicker than patients eligible to enroll in clinical trials, which usually require an ECOG performance status of 0 or 1. Nonetheless, as expected, patients with *EGFR*/*ALK*-positive nonsquamous NSCLC, most of whom received an *EGFR*/*ALK* TKI as first-line therapy, had substantially better OS than those with negative mutation status (median, 18 months vs 7 months from first-line initiation). The median OS from the initiation of second-line therapy for the *EGFR*/*ALK*-positive cohort was only 4 months. This may be because some patients with disease progression on first-line gefinitib received erlotinib in second-line.

This noninterventional study provides information on real-world patterns of treatment, biopsy, biomarker testing, and HCRU among patients with stage IIIB/IV NSCLC at several sites in Japan, including the continuum of therapy from first- through third-line regimens. In Japan, most drugs are reimbursed; therefore, doctors can choose therapeutic regimens without limitations imposed by insurance or expense considerations. Overall, 70% of patients with squamous NSCLC continued to second-line therapy, and 35% received third-line therapy; similar proportions to those reported by Minami et al[26] (66% and 33%, respectively) in their single-center study of Japanese patients with stage IIIB/IV squamous NSCLC in 2007–2015. Instead, 52% and 27% of patients in our study with *EGFR*/*ALK*-negative/unknown nonsquamous NSCLC received second-line and third-line therapy, respectively, somewhat lower proportions than reported by Minami et al[27] (61% and 34%, respectively) in their parallel study of *EGFR*-negative advanced lung adenocarcinoma. Our study differs from other prior observational studies in Japan, most of which were focused on evaluating outcomes with prespecified NSCLC therapies.[28–31]

The limitations of our study include those common to all retrospective chart review studies, such as potential transcription errors and missing data. In Japan, patient charts are not transferred when patients move to a new hospital; therefore, it is possible that some treatment regimens were incomplete, and thus not reflective of actual prescribing, if patients had changed hospital. While we provided training to abstractors and employed a standardized eCRF with prespecified variable definitions, we did not conduct pilot testing or an intra-rater reliability assessment. Other study limitations are the small sample size in some cohorts, giving wide OS and treatment duration ranges, and the lack of outcome data associated with specific therapies. Moreover, it would have been of interest to examine the prevalence of different *EGFR* mutation types; however, these data were not collected.

We included data from a convenience sample of patients at specialized study centers who presented with newly diagnosed stage IIIB/IV NSCLC and initiated first-line therapy, excluding those participating in clinical trials, thereby limiting the generalizability of our findings. Although our population does not represent the full Japanese population with NSCLC, our findings complement clinical trial data. We have described NSCLC treatment patterns by mutation status and age group, in line with the treatment guidelines, thus providing a benchmark for care provided in recent years.

These results from 2011 onward may not be reflective of the current clinical landscape. The treatment options for NSCLC are rapidly increasing with the emergence of checkpoint-based immunotherapies, such as pembrolizumab and nivolumab, and the newer targeted therapies, such as the third-generation *EGFR* TKIs (e.g., osimertinib) and the

second- and third-generation *ALK* inhibitors. The importance of predictive biomarker testing and the role of personalized treatment are increasingly relevant in light of these expanding treatment options. With the use of immunotherapies and ever-improving knowledge about targetable mutations, we believe there is cause for optimism regarding future therapy for advanced NSCLC based on our finding that patients in the nonsquamous cohort with *EGFR*/*ALK*-positive status, most of whom were treated with an *EGFR*/*ALK* TKI, had a median OS of 18 months, almost double that for the full study population (10 months).

In conclusion, we found that the majority of patients with nonsquamous NSCLC were tested for predictive biomarkers, most commonly for *EGFR* mutation. Treatment for both older patients and those with *EGFR*/*ALK*-positive nonsquamous NSCLC at these 5 sites in Japan is personalized according to mutation status and is in concordance with guideline recommendations.

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Disclosure

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Supplementary materials

Approving ethics committees

The study protocol conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013) and was approved by the head of each study site after review by the institutional ethics committee (EC).

Site	Site name in Japanese (official name)	Name of EC, translated into English	Name of EC in Japanese (official name)
KKR Sapporo Medical Center	KKR札幌医療センター	Ethics committee of KKR Sapporo Medical Center	KKR札幌医療センター倫理委員会
Tsuboi Cancer Center Hospital	一般財団法人慈山会医学研究所付属　坪井病院	Research review committee	研究審査委員会
Gunma Prefectural Cancer Center	群馬県立がんセンター	Ethics committee of Gunma Prefectural Cancer Center	群馬県立がんセンター倫理委員会
Tokyo Women's Medical University Yachiyo Medical Center	東京女子医科大学附属八千代医療センター	Ethics committee of Tokyo Women's Medical University	東京女子医科大学　倫理委員会
Kanagawa Cardiovascular and Respiratory Center	地方独立行政法人神奈川県立病院機構　神奈川県立循環器呼吸器病センター	Contract research review committee	受託研究審査委員会

Table S1 Treatment patterns for patients with advanced NSCLC, squamous histology[a]

Treatment regimen	Squamous cell NSCLC
First-line therapy	(N=43)
Platinum combination	36 (84)
Carboplatin, paclitaxel	22 (51)
Carboplatin, tegafur/gimeracil/oteracil[b]	3 (7)
Cisplatin, docetaxel	3 (7)
Cisplatin, vinorelbine	3 (7)
Single agent	6 (14)
Docetaxel	5 (12)
Carboplatin	1 (2)
EGFR/*ALK* TKI	1 (2)
Erlotinib	1 (2)
Second-line therapy	n=30
Platinum combination	8 (27)
Carboplatin, paclitaxel	2 (7)
Carboplatin, tegafur/gimeracil/oteracil	2 (7)
Carboplatin, vinorelbine	2 (7)
Carboplatin, docetaxel	1 (3)
Cisplatin, tegafur/gimeracil/oteracil	1 (3)
Single agent	20 (67)
Docetaxel	14 (47)
Gemcitabine	3 (10)
Pemetrexed	1 (3)
Tegafur/gimeracil/oteracil	2 (7)
EGFR/*ALK* TKI	2 (7)
Erlotinib	2 (7)
Third-line therapy	n=15
Platinum combination	1 (7)
Carboplatin, vinorelbine	1 (7)
Nonplatinum combination	2 (13)
Gemcitabine, vinorelbine	1 (7)
Albumin-bound paclitaxel, erlotinib	1 (7)
Single agent	11 (73)
Tegafur/gimeracil/oteracil	5 (33)
Pemetrexed	2 (13)
Docetaxel	1 (7)
Gemcitabine	1 (7)

(*Continued*)

Table S1 (*Continued*)

Treatment regimen	Squamous cell NSCLC
Paclitaxel	1 (7)
Vinorelbine	1 (7)
EGFR/*ALK* TKI	1 (7)
Erlotinib	1 (7)

Notes: Data are n (%). Percentages may not be additive because of rounding. [a]The top 4 to 5 regimens for each category are presented. [b]Oral anticancer drug composed of tegafur, gimeracil, and oteracil potassium at a molar ratio of 1:1:0.4.
Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Table S2 Treatment patterns for patients with advanced NSCLC, nonsquamous histology and *EGFR*/*ALK*-negative or unknown status, or not tested[a]

Treatment regimen	*EGFR*/*ALK* negative/unknown
First-line therapy	(N=83)
Platinum combination	74 (89)
Carboplatin, paclitaxel	22 (27)
Cisplatin, pemetrexed	10 (12)
Carboplatin, pemetrexed	8 (10)
Bevacizumab, carboplatin, paclitaxel	7 (8)
Cisplatin, gemcitabine	4 (5)
Single agent	9 (11)
Docetaxel	3 (4)
Paclitaxel	2 (2)
Tegafur/gimeracil/oteracil[b]	2 (2)
Carboplatin	1 (1)
Pemetrexed	1 (1)
Second-line therapy	n=43
Platinum combination	9 (21)
Carboplatin, paclitaxel	2 (5)
Cisplatin, pemetrexed	2 (5)
Bevacizumab, carboplatin, erlotinib, paclitaxel	1 (2)
Bevacizumab, carboplatin, paclitaxel	1 (2)
Bevacizumab, carboplatin, pemetrexed	1 (2)
Nonplatinum combination	2 (5)
Bevacizumab, pemetrexed	1 (2)
Gemcitabine, vinorelbine	1 (2)
Single agent	29 (67)
Docetaxel	15 (35)
Pemetrexed	14 (33)
EGFR/*ALK* TKI	3 (7)
Erlotinib	3 (7)
Third-line therapy	n=22
Platinum combination	7 (32)
Carboplatin, paclitaxel	3 (14)
Carboplatin, tegafur/gimeracil/oteracil	2 (9)
Albumin-bound paclitaxel, carboplatin	1 (5)
Albumin-bound paclitaxel, bevacizumab, carboplatin	1 (5)
Nonplatinum combination	1 (5)
Albumin-bound paclitaxel, erlotinib, gemcitabine, vinorelbine	1 (5)
Single agent	11 (50)
Docetaxel	5 (23)
Pemetrexed	4 (18)
Amrubicin HCl	1 (5)
Gemcitabine	1 (5)
EGFR/*ALK* TKI	3 (14)
Erlotinib	3 (14)

Notes: Data are n (%). Percentages may not be additive because of rounding. [a]The top 5 regimens for each category are presented. [b]Oral anticancer drug composed of tegafur, gimeracil, and oteracil potassium at a molar ratio of 1:1:0.4.
Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Table S3 Treatment patterns for patients with advanced NSCLC, nonsquamous histology and *EGFR*/*ALK*-positive status[a]

Treatment regimen	*EGFR*/*ALK* positive
First-line therapy	(N=46)
Platinum combination	4 (9)
Carboplatin, pemetrexed	2 (4)
Bevacizumab, carboplatin, paclitaxel	1 (2)
Carboplatin, paclitaxel	1 (2)
Single agent	1 (2)
Bevacizumab	1 (2)
EGFR/*ALK* TKI	41 (89)
Gefitinib	38 (83)
Erlotinib	1 (2)
Crizotinib	2 (4)
Second-line therapy	n=30
Platinum combination	13 (43)
Carboplatin, paclitaxel	5 (17)
Bevacizumab, carboplatin, pemetrexed	4 (13)
Carboplatin, pemetrexed	3 (10)
Bevacizumab, carboplatin, paclitaxel	1 (3)
Single agent	2 (7)
Pemetrexed	2 (7)
EGFR/*ALK* TKI	15 (50)
Erlotinib	11 (37)
Gefitinib	2 (7)
Afatinib	2 (7)
Third-line therapy	n=15
Platinum combination	3 (20)
Carboplatin, pemetrexed	2 (13)
Cisplatin, erlotinib, tegafur/gimeracil/oteracil[b]	1 (7)
Nonplatinum combination	2 (13)
Gefitinib, pemetrexed	1 (7)
Gemcitabine, vinorelbine	1 (7)
Single agent	1 (7)
Docetaxel	1 (7)
EGFR/*ALK* TKI	9 (60)
Erlotinib	9 (60)

Notes: Data are n (%). Percentages may not be additive because of rounding. [a]The top 5 regimens for each category are presented. [b]Oral anticancer drug composed of tegafur, gimeracil, and oteracil potassium at a molar ratio of 1:1:0.4.

Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Table S4 Treatment patterns for all patients with advanced NSCLC[a]

Treatment regimen	All patients
First-line therapy	(N=175)
Platinum combination	115 (66)
Carboplatin, paclitaxel	45 (26)
Cisplatin, pemetrexed	11 (6)
Carboplatin, pemetrexed	10 (6)
Bevacizumab, carboplatin, paclitaxel	8 (5)
Carboplatin, tegafur/gimeracil/oteracil[b]	5 (3)
Single agent	16 (9)
Docetaxel	8 (5)
Carboplatin	2 (1)
Paclitaxel	2 (1)
Tegafur/gimeracil/oteracil	2 (1)
Bevacizumab	1 (1)
Pemetrexed	1 (1)
EGFR/*ALK* TKI	44 (25)
Gefitinib	40 (23)
Erlotinib	2 (1)
Crizotinib	2 (1)

(*Continued*)

Table S4 (*Continued*)

Treatment regimen	All patients
Second-line therapy	n=105
Platinum combination	30 (29)
Carboplatin, paclitaxel	9 (9)
Bevacizumab, carboplatin, pemetrexed	5 (5)
Carboplatin, pemetrexed	3 (3)
Carboplatin, tegafur/gimeracil/oteracil	3 (3)
Bevacizumab, carboplatin, paclitaxel	2 (2)
Nonplatinum combination	2 (2)
Bevacizumab, pemetrexed	1 (1)
Gemcitabine, vinorelbine	1 (1)
Single agent	51 (49)
Docetaxel	29 (28)
Pemetrexed	17 (16)
Gemcitabine	3 (3)
Tegafur/gimeracil/oteracil	2 (2)
EGFR/*ALK* TKI	22 (21)
Erlotinib	17 (16)
Gefitinib	2 (2)
Afatinib	2 (2)
Crizotinib	1 (1)
Third-line therapy	n=54
Platinum combination	12 (22)
Carboplatin, paclitaxel	4 (7)
Carboplatin, pemetrexed	2 (4)
Carboplatin, tegafur/gimeracil/oteracil	2 (4)
Albumin-bound paclitaxel, bevacizumab, carboplatin	1 (2)
Albumin-bound paclitaxel, carboplatin	1 (2)
Nonplatinum combination	5 (9)
Gemcitabine, vinorelbine	2 (4)
Albumin-bound paclitaxel, erlotinib	1 (2)
Albumin-bound paclitaxel, erlotinib, gemcitabine, vinorelbine	1 (2)
Gefitinib, pemetrexed	1 (2)
Single agent	23 (43)
Docetaxel	8 (15)
Pemetrexed	6 (11)
Gemcitabine	2 (4)
Paclitaxel	1 (2)
Vinorelbine	1 (2)
Tegafur/gimeracil/oteracil	5 (9)
EGFR/*ALK* TKI	13 (24)
Erlotinib	13 (24)

Notes: Data are n (%). Percentages may not be additive because of rounding. [a]The top 5 regimens for each category are presented. [b]Oral anticancer drug composed of tegafur, gimeracil, and oteracil potassium at a molar ratio of 1:1:0.4.

Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.