

Biomarker testing for personalized, first-line therapy in advanced nonsquamous non-small cell lung cancer patients in the real world setting in Japan: a retrospective, multicenter, observational study (the BRAVE study)

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Abstract

Background: Molecular diagnostic testing is necessary to guide optimal first-line treatment. The number of patients who receive first-line treatment based on biomarker analysis in Japan is unknown. We aimed to determine the proportion of nonsquamous non-small cell lung cancer (NSCLC) patients for whom first-line treatment was selected based on biomarker testing.

Methods: This retrospective, multicenter, observational study registered patients aged ≥ 20 years with locally advanced or metastatic nonsquamous NSCLC who started first-line treatment between August and December 2017 in Japan. Data were collected from medical records between January and May 2018. The primary endpoint was the proportion of patients with confirmed biomarker status for first-line treatment decision.

Results: Among 202 patients enrolled from 11 centers, 161 (79.7%; 95% confidence interval, 74.2–85.2%) had confirmed biomarker status. The testing rate was highest for epidermal growth factor receptor (*EGFR*; 97.5%), followed by anaplastic lymphoma kinase (*ALK*; 88.1%), programmed death ligand-1 (PD-L1; 87.1%), and *ROS1* (67.3%). For first-line treatment, 70/75 patients with *EGFR*-positive tumors were administered an *EGFR*-TKI; 14/15 patients with *ALK*-positive tumors received an *ALK* inhibitor; 2/2 patients with *ROS1*-positive tumors received a *ROS1* inhibitor; and 29/36 driver mutation-negative patients with a PD-L1 tumor proportion score $\geq 50\%$ were administered an anti-PD-1 monoclonal antibody. Median times from confirmed diagnosis date to first-line treatment initiation, and from first biomarker test order to last biomarker test result were 19 and 11 days, respectively.

Conclusions: The proportion of nonsquamous NSCLC patients with confirmed biomarker status for first-line treatment was considered insufficient and in need of improvement.

Keywords: anaplastic lymphoma kinase, epidermal growth factor receptor, programmed death-ligand 1, *ROS1*

Received: 3 July 2019; revised manuscript accepted: 6 January 2020.

Introduction

According to recent statistics, lung cancer is among the most common cancers in both men

[84,500 cases (15%)] and women [40,600 cases (9%)] in Japan.¹ In 2018, lung cancer was the leading cause of cancer deaths among men

Ther Adv Med Oncol

2020, Vol. 12: 1–9

DOI: 10.1177/
1758835920904522

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[55,100 deaths (25%)], and the second leading cause of cancer deaths after colon/rectum cancer among women [22,400 deaths (14%)] in Japan.¹

Although there have been recent advances in the development of molecular-targeted agents and immunotherapy for lung cancer, these agents are effective only in patients with targeted molecular biological characteristics. Cytotoxic chemotherapy, molecular-targeted therapy [epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS proto-oncogene 1 (ROS1) inhibitors], and immune checkpoint inhibitors [anti-programmed cell death protein-1 (PD-1) antibody] have been approved as first-line treatment for advanced nonsquamous non-small cell lung cancer (NSCLC) patients in Japan.

Molecular biomarker testing is necessary to guide the selection of optimal first-line treatment with demonstrated effectiveness against the molecular defects relevant to each individual patient. Some molecular biomarker tests were available in daily clinical practice in Japan. Specifically, the following molecular biomarker tests were used in Japan in conjunction with laboratory-developed tests for the detection of several markers: the cobas® EGFR Mutation Test (Roche Diagnostics, Indianapolis, IN, USA) for the detection of *EGFR* mutations as a companion diagnostic test with EGFR-tyrosine kinase inhibitors (EGFR-TKIs), the Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories, Chicago, IL, USA), and the Histofine ALK iAEP kit (Nichirei Bioscience, Tokyo, Japan) for the detection of *ALK* as companion diagnostic tests with ALK inhibitors, the OncoGuide AmoyDx ROS1 gene fusions detection kit (Amoy Diagnostics Co Ltd., Xiamen, China) for the detection of *ROS1* as a companion diagnostic test with ROS1 inhibitors, and the programmed death-ligand 1 (PD-L1) IHC 22C3 pharmDx and PD-L1 IHC 28-8 pharmDx (Dako, Carpinteria, CA, USA) for the detection of PD-L1 as companion diagnostic tests with anti-PD-1 monoclonal antibodies.

The 2018 Guideline for Treatment of Lung Cancer of The Japan Lung Cancer Society recommends testing patients with nonsquamous NSCLC for multiple biomarkers, including *EGFR* gene mutation, *ALK* fusion, *ROS1* fusion, PD-L1 expression, and *BRAF* gene mutation.² However, these biomarker tests cannot be performed in some patients with advanced NSCLC because tissue

samples are insufficient for performing multiple biomarker tests.³ Furthermore, tissue samples do not always contain sufficient tumor cells for the detection of such biomarkers. If biomarker tests are performed sequentially, some patients might have to wait to start first-line treatment until all the biomarker test results are available.

The number of patients who receive personalized first-line treatment based on the results of biomarker analysis in the real clinical setting in Japan is unknown. The present study aimed to determine the proportion of nonsquamous NSCLC patients for whom first-line treatment was selected based on biomarker testing results by investigating biomarker testing status before starting first-line treatment.

Methods

Study design

In this retrospective, multicenter, observational study, data were collected from the clinical records of patients with locally advanced or metastatic nonsquamous NSCLC in Japan. Subjects were asked for consent and data were collected from January 2018 to May 2018. The last patient's last visit was in May 2018, and the database was locked in July 2018.

The following data were collected from patients' clinical records: patients' clinical background, sample collection, biomarker testing, and selection of first-line treatment. To avoid selection bias at the time of enrollment, patients who were eligible for this study were enrolled in a consecutive and sequential manner.

The study protocol was approved by the ethical review board and the institutional review board of each participating medical center, the names of which are presented, with approval numbers, in online supplementary Table 1. The study adhered to the guidelines set forth by the Declaration of Helsinki, and study patients provided written informed consent at study enrollment. In cases when patients could not be contacted owing to their death, change of residence, or other cause, patients were enrolled in this study by an appropriate method that was deemed equivalent to obtaining consent from the patients, in accordance with the decisions of the institutional review board at each center.

Patients

Patients aged ≥ 20 years at the time of informed consent, with locally advanced or metastatic non-squamous NSCLC, who did not have an indication for radical surgery or radiotherapy, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, and who started first-line treatment between 1 August 2017 and 31 December 2017, were included in this study. Patients with postoperative recurrence, those enrolled in clinical trials of an unapproved drug as first-line therapy for advanced NSCLC, and those otherwise considered unsuitable to participate in this study by the investigators at the study sites were excluded.

Endpoints

The primary endpoint was the proportion of patients with confirmed biomarker status for first-line treatment decision. According to the 2016 Guideline for Treatment of Lung Cancer of The Japan Lung Cancer Society,⁴ the primary endpoint was defined as the proportion of patients who met criteria A, B, or C, as follows: (A) patients who tested positive for at least *EGFR*, *ALK*, or *ROS1* gene alteration prior to starting first-line treatment; (B) patients who tested negative for all *EGFR*, *ALK*, and *ROS1* gene alterations and had a PD-L1 tumor proportion score (TPS) $\geq 50\%$ prior to starting first-line treatment; or (C) patients who tested negative for all *EGFR*, *ALK*, and *ROS1* gene alterations and had a PD-L1 TPS $< 50\%$ prior to starting first-line treatment. The secondary endpoints were the proportion of patients who underwent each biomarker test, the proportion of patients who tested positive for each biomarker, the combination and order of biomarker tests performed, selection of first-line treatment, and time to initiation of first-line treatment. In this study, the driver mutations, that is, those that confer a growth advantage on the cancer cell,⁵ specifically assessed were those for *EGFR*, *ALK*, and *ROS1*.

Statistical analysis

Sample size based on statistical power was not calculated because this was a descriptive study. This study aimed to enroll 200 patients from 10 to 15 sites in Japan, as this was considered the number of cases that could be collected during the study period. Although the width of a confidence interval (CI) depends on a true value of the primary

Table 1. Patient characteristics.

		<i>n</i> = 202
Sex	Male	126 (62.4)
Age, years	Median (range)	70.0 (32–89)
Smoking status	Current smoker	30 (14.9)
	Never smoker	67 (33.2)
	Past smoker	105 (52.0)
ECOG PS	0	63 (31.2)
	1	139 (68.8)
Clinical stage	IIIA	7 (3.5)
	IIIB	21 (10.4)
	IIIC	6 (3.0)
	IVA	82 (40.6)
	IVB	85 (42.1)
	Missing	1 (0.5)
Histological type	Adenocarcinoma	183 (90.6)
	Other ^a	19 (9.4)

Data are presented as *n* (%) unless otherwise stated.
^aLarge cell carcinoma: three patients; neuroendocrine tumor of the lung: two patients; NSCLC not otherwise specified: 14 patients.
 ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer.

endpoint, this sample size would yield a CI of a width of $< 15\%$ for any value of a plausible range of the primary endpoint. Descriptive statistics were used for baseline demographic and clinical characteristics, with *n* (%) for categorical variables and median (range) for continuous variables. All endpoints were summarized descriptively. Base SAS[®] Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

Patients

A total of 202 patients were enrolled from 11 medical centers in Japan. Patients had a median age of 70 (range, 32–89) years and 62.4% were male (Table 1). Most patients (68.8%) had an ECOG PS of 1 and were classified as having adenocarcinoma histological type (90.6%).

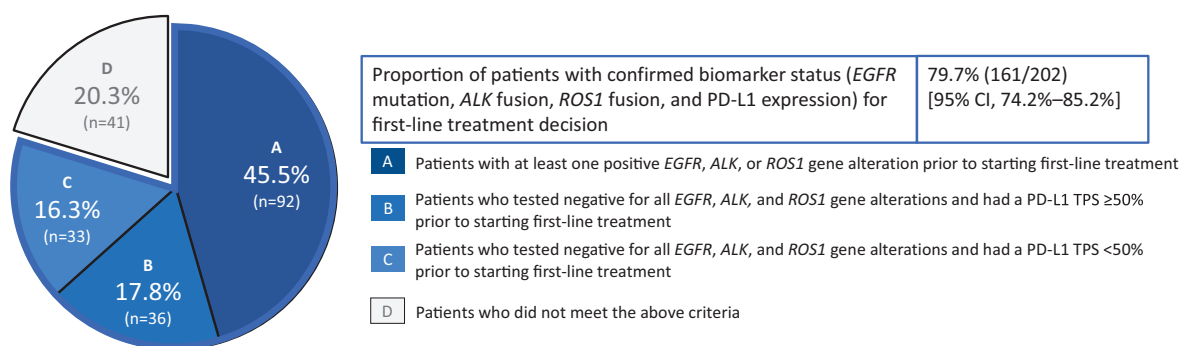


Figure 1. Proportion of patients with confirmed biomarker status (*EGFR* mutation, *ALK* fusion, *ROS1* fusion, and PD-L1 expression) for first-line treatment decision.

ALK, anaplastic lymphoma kinase; CI, confidence interval; *EGFR*, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; *ROS1*, ROS proto-oncogene 1; TPS, tumor proportion score.

Table 2. Details of 41 patients who did not meet criteria for the primary endpoint.

Reasons	n	Details
Unidentified driver mutation ^a status	29	<i>ROS1</i> test not performed: 23 Other: 6
Confirmed driver mutation-negative but PD-L1 test not performed	4	–
Unidentified driver mutation and PD-L1 status	6	All testing was not performed: 2 <i>ROS1</i> and PD-L1 were not performed: 3 <i>ALK</i> and PD-L1 were not performed: 1
All biomarker testing was performed but some testing results were invalid.	2	Invalid <i>ROS1</i> result: 1 Invalid PD-L1 result: 1

^aDriver mutations: *EGFR*, *ALK*, *ROS1*.
ALK, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; *ROS1*, ROS proto-oncogene 1.

Endpoints

The proportion of patients with confirmed biomarker status for first-line treatment decision (primary endpoint) was 79.7% (95% CI, 74.2–85.2%) (Figure 1). The proportions of patients who met criteria A, B, and C were 45.5%, 17.8%, and 16.3%, respectively. Of 202 patients, 41 (20.3%) did not meet the criteria for the primary endpoint (Table 2).

The proportions of patients who underwent biomarker testing for *EGFR*, *ALK*, *ROS1*, and PD-L1 were 97.5%, 88.1%, 67.3%, and 87.1%, respectively (Figure 2). A total of 206 *EGFR* tests were performed, among which 118 (57.3%) tissue samples were used for testing. A total of 212 *ALK* tests were performed, among which 164 (77.4%) tissue samples were used for testing. A

total of 158 *ROS1* tests were performed, among which 101 (63.9%) tissue samples were used for testing. A total of 204 PD-L1 tests were performed, among which 170 (83.3%) tissue samples were used for testing. Nontissue samples used included cytology samples and cell blocks. The proportions of patients who tested positive for *EGFR*, *ALK*, and *ROS1* were 38.1%, 8.4%, and 1.5%, respectively (Figure 2). The proportions of patients with PD-L1 TPS <1%, 1–49%, and \geq 50% were 33.0%, 24.4%, and 40.3%, respectively. The driver mutations for *EGFR*, *ALK*, and *ROS1* were mutually exclusive.

Among 76 patients who were driver mutation-positive and underwent PD-L1 testing, 38.2% (29/76), 32.9% (25/76), and 25.0% (19/76) had a PD-L1 TPS <1%, 1–49%, and \geq 50%, respectively; 3.9%

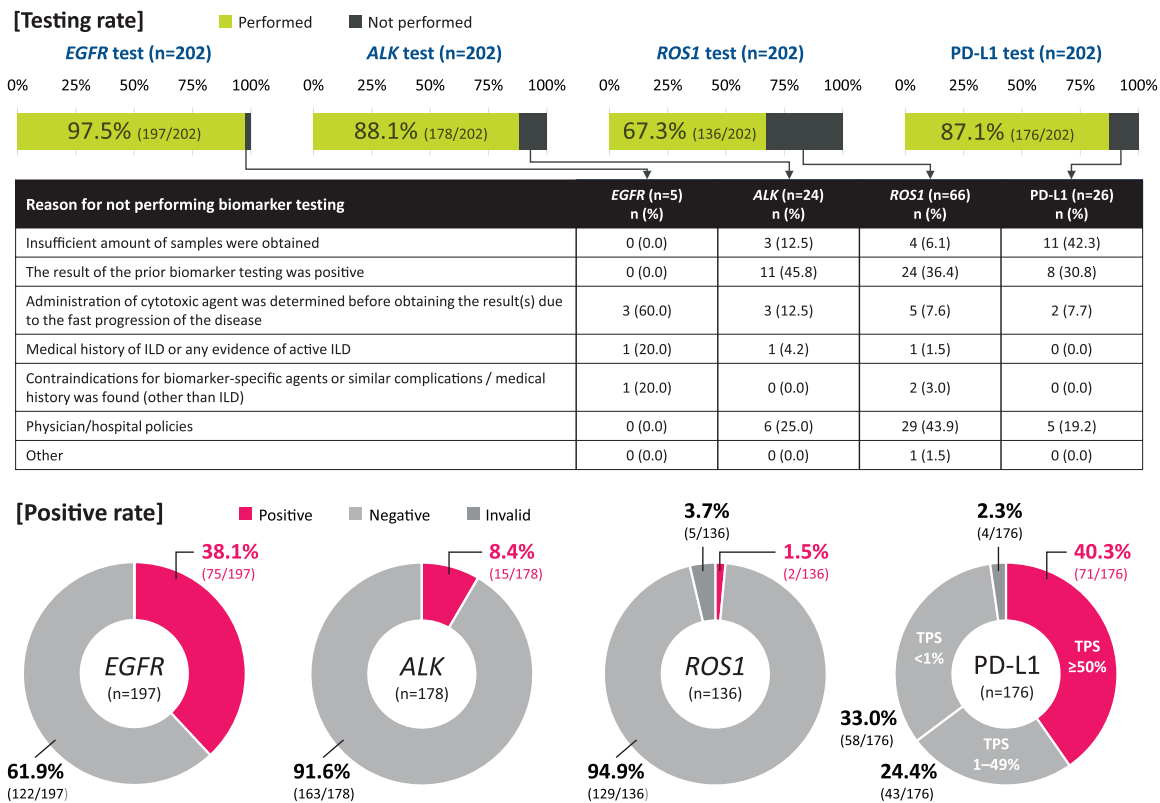


Figure 2. Testing rate and positive rate for each biomarker.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; PD-L1, programmed death-ligand 1; ROS1, ROS proto-oncogene 1; TPS, tumor proportion score.

(3/76) had invalid test results. Among 70 patients who were driver mutation-negative and underwent PD-L1 testing, 28.6% (20/70), 18.6% (13/70), and 51.4% (36/70) had a PD-L1 TPS <1%, 1–49%, and ≥50%, respectively; 1.4% (1/70) had invalid test results.

The patterns of biomarker testing performed are shown in Table 3. The most common testing pattern was concurrent testing of *EGFR*, *ALK*, *ROS1*, and PD-L1 (64/202, 31.7%), followed by concurrent testing of *EGFR*, *ALK*, and PD-L1 (37/202, 18.3%).

The selection of first-line treatment by biomarker status is shown in Table 4. Among the 75 patients who tested positive for *EGFR*, 93.3% (70/75) received first-line treatment with an EGFR-TKI. Among the 15 patients who tested positive for *ALK*, 93.3% (14/15) received first-line treatment with an ALK inhibitor. The patients who tested positive for *ROS1* (100%) received first-line treatment with a ROS1 inhibitor. Among the 36 patients who were driver mutation-negative and had a PD-L1 TPS ≥50%, 80.6% (29/36) received

first-line treatment with an anti-PD-1 monoclonal antibody. All 33 patients (100%) who were driver mutation-negative and had a PD-L1 TPS <50% received first-line treatment with chemotherapy.

The median time from the date of confirmed diagnosis to initiation of first-line treatment was 19.0 (range, 0–232) days ($n=202$). The median time between ordering the first biomarker test and receiving the last biomarker test result was 11.0 (range, 2–67) days ($n=197$).

Discussion

Previous studies have investigated multiple biomarker testing rates and treatment patterns in NSCLC patients.^{6–9} However, to the best of our knowledge, the present study is the first to focus on the proportion of advanced nonsquamous NSCLC patients with confirmed biomarker status for first-line treatment decision.

The proportion of patients with confirmed biomarker status for first-line treatment decision was

Table 3. Patterns of biomarker testing performed.

Number of biomarker tests performed	n (%)	Pattern of biomarker testing performed	n (%)
4	119 (58.9)	<i>EGFR/ALK/ROS1</i> /PD-L1	64 (31.7)
		<i>EGFR/ALK/ROS1</i> ⇒ PD-L1	15 (7.4)
		<i>EGFR/ALK</i> /PD-L1 ⇒ <i>ROS1</i>	11 (5.4)
		<i>EGFR</i> ⇒ <i>ALK</i> /PD-L1/ <i>ROS1</i>	6 (3.0)
		Other (a total of 13 patterns)	23 (11.4)
3	57 (28.2)	<i>EGFR/ALK</i> /PD-L1	37 (18.3)
		<i>EGFR/ALK/ROS1</i>	7 (3.5)
		Other (a total of eight patterns)	13 (6.4)
2	16 (7.9)	<i>EGFR</i> /PD-L1	5 (2.5)
		Other (a total of five patterns)	11 (5.4)
1	8 (4.0)	<i>EGFR</i>	6 (3.0)
		PD-L1	2 (1.0)
0	2 (1.0)	–	2 (1.0)

Arrow (⇒) indicates sequential order of tests. Virgule (/) indicates concurrent testing.
 ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; ROS1, ROS proto-oncogene 1.

79.7% (161/202). Regarding the testing rate for individual biomarkers, the testing rate was highest for *EGFR* (97.5%), followed by *ALK* (88.1%) and PD-L1 (87.1%), and was lowest for *ROS1* (67.3%). The main reasons for no biomarker testing were physician or hospital policies regarding *ROS1* testing (29/66 patients) and *ALK* testing (6/24 patients), and insufficient sample amount for PD-L1 testing (11/26 patients). ‘Physician/hospital policies’ was a relatively frequent reason for a lack of *ROS1* and *ALK* testing. We consider that a possible explanation for this is the relatively low frequency of these mutations. In Japanese lung adenocarcinoma cases, the frequency of *ALK* mutation was reported to be 3.9% and that for *ROS1* mutation, 1.2%.¹⁰ Of note, *ROS1* testing (companion diagnostics for *ROS1* testing; ROS1 fusion gene detection kit, Amoy Diagnostics, Xiamen, China) was launched in Japan in June 2017. Because the patients enrolled in this study initiated first-line treatment between August and December 2017, it is possible that the recently approved *ROS1* testing method was not widely performed at the time of the study. This may explain the low rate of *ROS1* testing in the

present study. Another potential reason for this is that, in some centers, testing for *ROS1* is conducted only if the results for *EGFR* and *ALK* testing are negative, as these tests are mutually exclusive. If we consider an additional 15 patients who were treated with an anti-PD-1 monoclonal antibody based on PD-L1 test results (Table 4) without undergoing *ROS1* testing, the proportion of patients increases to 87.1% [(161 + 15 = 176)/202]. The most common testing pattern was concurrent testing of *EGFR*, *ALK*, *ROS1*, and PD-L1 (31.7%) followed by concurrent testing of *EGFR*, *ALK*, and PD-L1 (18.3%). The median time from diagnosis to initiation of first-line treatment was 19 days, and the median turnaround time for overall biomarker testing was 11 days. Finally, among the 161 patients with confirmed biomarker status, 148 (91.9%) received appropriate biomarker-based treatment.

In the PivOTAL study,⁶ a multinational retrospective study of molecular testing and treatment patterns in patients with advanced NSCLC, among the 129 Japanese patients included, the

Table 4. First-line treatment by biomarker status.

	EGFR-TKI	ALK inhibitor	ROS1 inhibitor	Anti-PD-1 mAb	Chemotherapy
<i>EGFR</i> (+) (<i>n</i> = 75)	70 ^a (93.3%)	0	0	1 (1.3%)	4 (5.3%)
<i>ALK</i> (+) (<i>n</i> = 15)	0	14 (93.3%)	0	0	1 (6.7%)
<i>ROS1</i> (+) (<i>n</i> = 2)	0	0	2 (100.0%)	0	0
All driver mutation-negative and PD-L1 ≥50% (<i>n</i> = 36)	0	0	0	29 (80.6%)	7 (19.4%)
All driver mutation-negative and PD-L1 <50% (<i>n</i> = 33)	0	0	0	0	33 (100.0%)
Other ^c (<i>n</i> = 41)	0	0	0	15 ^b (36.6%)	26 (63.4%)

Grey shading: Confirmed biomarker status and received biomarker-based treatment.
Percentages are based on each row total.
^aA total of 64 patients were treated with EGFR-TKI monotherapy and six patients were treated with EGFR-TKI plus antivascular endothelial growth factor monoclonal antibody.
^bAll 15 patients had PD-L1 tumor proportion score ≥50% but unknown *ROS1* status.
^cPatients who did not meet any of the criteria described above.
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; ROS1, ROS proto-oncogene 1; TKI, tyrosine kinase inhibitor.

molecular testing rate was 81% for *EGFR* mutation and 19% for *ALK* rearrangement (*versus* 97.5% and 88.1%, respectively, in the present study). A possible reason for the higher *ALK* testing rate in the present study is that there is a greater awareness among clinicians and institutions of the current evidence-based guidelines on the subject and the overall importance of molecular testing in order to adequately select the best targeted therapy for patients. It should be noted that the PivOTAL study was performed between 2011 and 2013, and that *ALK* inhibitors were first approved in Japan in 2012. Therefore, clinicians may have believed *ALK* testing to be unnecessary or they may not have been aware of this test before the approval of *ALK* inhibitors.

Consistent with the results of the present study, another previous multinational retrospective chart review conducted in the US and European countries that evaluated trends in NSCLC biomarker testing rates found that the majority of patients underwent *EGFR* and *ALK* testing.⁸ In the present study, the testing rate was highest for *EGFR* compared with that for *ALK*, PD-L1, and *ROS1*. These results are consistent with those of

the PivOTAL study, which showed that in all countries included in the study, the *EGFR* testing rate was higher than those of other molecular tests. The proportions of patients in Japan who tested positive for *EGFR* and *ALK* in the PivOTAL study were 42% and 8%, respectively; these values were consistent with those in the present study (38.1% and 8.4%, respectively).

The selection of first-line treatment with an EGFR-TKI, *ALK* inhibitor, and *ROS1* inhibitor was performed in 93.3%, 93.3%, and 100% of patients who tested positive for the respective biomarker in the present study. These values were consistent with those reported in a previous retrospective study, which found that 96.8% (*n* = 61) of patients presenting with an actionable *ALK*, *EGFR*, or *ROS1* mutation were prescribed an appropriate targeted therapy.⁹ Ideally, the proportion of patients with confirmed biomarker status for first-line treatment decision would be 100%. However, this survey revealed that, in 20% of patients, the first-line treatment was selected even though their biomarker status was not confirmed. The biomarker testing rate was considered unsatisfactory; in particular, the *ROS1*

testing rate was low in the present study. To improve this rate in the real-world clinical setting in Japan, awareness of *ROS1* testing should be increased among physicians because the low *ROS1* testing rate was due to physician/hospital policies. In addition, an adequate amount of tissue samples should be obtained for multiple biomarker testing, given that the low PD-L1 testing rate in this study was attributed to an insufficient amount of samples obtained.

A single-center study by Yu and colleagues evaluated single-gene testing *versus* multiple biomarker testing rates using Oncomine Dx Target Test for advanced NSCLC.⁷ The Oncomine Dx Target Test is a next-generation sequencing (NGS) panel for NSCLC testing, which could facilitate access to multiple biomarker testing using small tissue samples. In general, NGS can detect a number of gene alterations concurrently using a single sample. In contrast, the biomarker testing methods used in the present study require a sample each. Thus, the use of NGS methods might be useful in terms of saving tissue samples, or in instances in which tissue samples are too small for multiple biomarker tests. Therefore, the detection of gene alterations using NGS might lead to an increased proportion of patients with confirmed biomarker status at the time of selecting the first-line therapy.

The present study has some limitations, such as the relatively small sample size of 202, the brief study period of 5 months, the retrospective study design, and the descriptive nature of the findings. The timing of the study was another limitation as *ROS1* was not widely performed at the time the patients were diagnosed and first treated. Furthermore, reimbursement for *ROS1* testing became available in Japan on 1 June 2017, and this may have contributed to the low *ROS1* testing rate in the present study. Another limitation related to the timing of the study is that the present findings may become less relevant as new approaches, such as multiplex testing and NGS, become more widely used. In addition, this study has limited generalizability in terms of extrapolating the results to the wider Japanese population because the investigational sites were specialized centers and the results may not reflect the approaches to biomarker testing at nonspecialist centers. Finally, as this study focused on the proportion of patients for whom first-line treatment was selected based on biomarker testing results, we did not collect treatment efficacy outcome data.

In conclusion, compared with other biomarkers [*ALK* (88.1%), PD-L1 (87.1%), and *ROS1* (67.3%)], the highest testing rate was that for *EGFR* (97.5%). As a result, the proportion of nonsquamous NSCLC patients with confirmed biomarker status for first-line treatment decision was 79.7%. We consider that this proportion is still insufficient and in need of improvement. To increase the proportion of NSCLC patients with confirmed biomarker status, it is important to conduct genetic testing, even to detect genetic mutations with a lower mutation rate. In addition, it is necessary to collect sufficiently large tumor specimens to conduct multiple biomarker tests. Furthermore, to clarify the optimal strategy of biomarker testing for NSCLC patients in real clinical practice, it is necessary that future studies apply recently developed biomarker testing methods, such as NGS.

Acknowledgements

The authors would like to thank the patients and their families, as well as the staff and investigators at all of the participating study sites. The authors would like to thank Michelle Belanger, of Edanz Medical Writing for providing medical writing services, which were funded by AstraZeneca through EMC K.K. in accordance with Good Publication Practice (GPP3) guidelines (<http://www.ismpp.org/gpp3>).

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and publication of this article: This study was sponsored by AstraZeneca.

Conflict of interest statement

K Nishino declares receiving personal fees from AstraZeneca, and, outside this work, personal fees from Chugai Pharmaceutical and Boehringer Ingelheim. T Kurata declares receiving a grant from AstraZeneca for study funding, and, outside this work, personal fees (honoraria) from AstraZeneca, MSD, Eli Lilly, Ono Pharmaceutical, Bristol, and MSD. Y Itoh, Y Yoshimura, and Y Yabuki are employees of AstraZeneca K.K. Outside this work, J Shimizu has received personal fees (speaker's bureau fees) from AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, MSD, Taiho Pharmaceutical, and Novartis Pharma. Outside this work, H Saito has received grants from Chugai Pharmaceutical, AstraZeneca, and MSD, and personal fees from Ono Pharmaceutical, Nippon Boehringer Ingelheim,

and Novartis Pharma. Outside this work, H Dosaka-Akita has received grants from Taiho Pharmaceutical Co., Ltd., Eli Lilly Japan K. K., and Ono Pharmaceutical Co., Ltd., and personal fees from AstraZeneca and Chugai Pharmaceutical Co., Ltd. K Masago declares no conflict of interest.

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Supplementary material

Supplemental material for this article is available online.

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