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ORIGINAL ARTICLE

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Systemic therapy treatment patterns in patients with advanced non-small cell lung cancer (NSCLC): PIvOTAL study

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The aim of this multinational retrospective cohort study, conducted at academic and community oncology centres, was to describe real-world treatment patterns for patients with a confirmed diagnosis of advanced/metastatic (stage IIIB/IV) non-small cell lung cancer (NSCLC) who initiated first-line systemic therapy from January 2011 through June 2014. The study included 1265 patients in Italy, Spain, Germany, Australia, Korea, Taiwan and Brazil. The proportion of patients with squamous versus non-squamous NSCLC was approximately 20% versus 75%, and associated patient demographic characteristics were similar in all countries, excepting race. Patients with squamous NSCLC were predominantly male and current/ex-smokers. Biomarker tests were performed for the majority of patients with non-squamous NSCLC, ranging from 54% (Brazil) to 91% in Taiwan, where, of those tested, 68% with non-squamous NSCLC had positive epidermal growth factor receptor (*EGFR*)-mutation status; in other countries the *EGFR*-positive percentages ranged from 17% (Spain/Brazil) to 40% (Korea). Platinum-based regimens were the most common first-line therapy in all countries except Taiwan, where gefitinib was the most common first-line agent. Median overall survival ranged from 9.3 months (Brazil) to 25.5 months (Taiwan). The diagnostic and treatment patterns recorded in this study were heterogeneous but largely in line with NSCLC guidelines during the study period.

KEYWORDS
international, non-small cell lung cancer, observational, survival, treatment patterns

1 | INTRODUCTION

Lung cancer is the most deadly cancer worldwide, often diagnosed when locally advanced (stage IIIB) or with distant metastases (stage IV). In 2012, lung cancer was responsible for 1.6 million deaths, amounting to about 20% of all cancer-related deaths (International Agency for Research on Cancer, 2014). The 5-year survival rates for lung cancer in 2005–2009 ranged from 15% to 20% in most countries (Cheng et al., 2016; Wang et al., 2013). Non-small cell lung cancer (NSCLC) is the most common histological type, comprising approximately 80%–85% of cases (Herbst, Heymach, & Lippman, 2008; Reck, Heigener, Mok, Soria, & Rabe, 2013). While the distribution of histologies varies among countries, the two most common NSCLC histological subtypes are squamous cell carcinoma and the non-squamous cell carcinomas, of which adenocarcinoma is the most common. However, a variable proportion of NSCLC remains unclassified histologically when the diagnosis relies on cytology or small biopsies (Travis et al., 2015). The majority of patients with lung cancer have a history of smoking, including from 65%–90% of men and 25%–70% of women, depending on the country (Cheng et al., 2016).

Many advances have been made in lung cancer screening, diagnostics, and therapy since the turn of the last century. Discoveries of targetable gene mutations and the development of targeted therapies, as well as immunotherapies such as the programmed death-1 (PD-1) and PD ligand-1 (PD-L1) inhibitors, have contributed to changes in the management of NSCLC. The potential now exists for personalised therapy based on histology and biomarker findings, raising hopes of improved outcomes for patients with lung cancer (Novello et al., 2016).

An understanding of real-world treatment patterns for NSCLC can provide context for the rapidly changing landscape of NSCLC therapy. Moreover, patients enrolled in randomised controlled trials (RCTs) do not represent patients seen in routine clinical practice who are often more diverse, have more comorbidities, and may not be eligible to participate in RCTs (Murthy, Krumholz, & Gross, 2004; Prince, Atenafu, & Krzyzanowska, 2015; Sekine, Takada, Nokihara, Yamamoto, & Tamura,

TABLE 1 Demographic and clinical characteristics of patients with advanced NSCLC in Italy, Spain and Germany

	Italy (*N* = 174)			Spain (*N* = 202)			Germany (*N* = 139)		
Characteristic	**SCC**	**NSCC**	**Unk**	**SCC**	**NSCC**	**Unk**	**SCC**	**NSCC**	**Unk**
Histology, *n* (%)	42 (24)	121 (70)	11 (6)	33 (16)	140 (69)	29 (14)	28 (20)	108 (78)	3 (2)
Male patients, *n* (%)	38 (90)	78 (64)	7 (64)	30 (91)	104 (74)	21 (72)	22 (79)	50 (46)	2 (67)
Age, mean (*SD*), years	67.4 (10.3)	63.3 (10.8)	68.0 (11.3)	62.8 (10.7)	62.8 (10.2)	63.2 (10.2)	64.7 (9.3)	62.7 (10.8)	58.3 (22.5)
Age range, years	39–83	28–86	50–86	40–84	41–84	44–81	42–77	39–81	33–76
Race, *n* (%)									
Caucasian	42 (100)	120 (99)	11 (100)	32 (97)	138 (99)	29 (100)	28 (100)	108 (100)	3 (100)
Black	0	0	0	0	2 (1)	0	0	0	0
Unknown	0	1 (1)	0	1 (3)	0	0	0	0	0
BMI categories, *n* (%)[a]									
Underweight	0	4 (3)	1 (9)	3 (9)	5 (4)	0	0	8 (7)	0
Normal	16 (38)	48 (40)	7 (64)	17 (52)	67 (48)	12 (41)	11 (39)	49 (45)	0
Overweight	19 (45)	39 (32)	1 (9)	9 (27)	49 (35)	14 (48)	12 (43)	39 (36)	1 (33)
Obese	1 (2)	17 (14)	0	3 (9)	12 (9)	1 (3)	5 (18)	11 (10)	2 (67)
Unknown	6 (14)	13 (11)	2 (18)	1 (3)	7 (5)	2 (7)	0	1 (1)	0
History of smoking, *n* (%)									
Current	12 (29)	22 (18)	3 (27)	13 (39)	41 (29)	13 (45)	11 (39)	37 (34)	0
Former	25 (60)	52 (43)	4 (36)	19 (58)	75 (54)	11 (38)	12 (43)	33 (31)	2 (67)
Never	1 (2)	28 (23)	4 (36)	1 (3)	22 (16)	5 (17)	0	22 (20)	1 (33)
Unknown	4 (10)	19 (16)	0	0	2 (1)	0	5 (18)[b]	16 (15)	0
Selected comorbidities, *n* (%)[c]									
COPD	10 (24)	8 (8)	1 (11)	5 (17)	24 (21)	2 (8)	9 (33)	33 (33)	0
Cardiovascular disease	12 (29)	26 (25)	2 (22)	6 (21)	25 (22)	2 (8)	8 (30)	21 (21)	0
Diabetes mellitus	6 (15)	24 (23)	2 (22)	3 (10)	15 (13)	6 (25)	5 (19)	11 (11)	0

The "Unknown" category includes patients for whom data were incomplete or missing. Percentages may not total 100 because of rounding.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; NSCC, non-squamous cell carcinoma; Unk, unknown histology.
[a]BMI categories were defined as follows (in kg/m^2): underweight, ≤18.49; normal, 18.50–24.99; overweight, 25.00–29.99; obese, ≥30.00.
[b]Three patients in the squamous cohort in Germany were recorded as being smokers without a specification as to current or former smoking; therefore, these patients were included in the unknown category.
[c]Comorbidities are reported for patients with non-missing data, including 153, 169 and 128 in Italy, Spain and Germany, respectively.

TABLE 2 Demographic and clinical characteristics of patients with advanced NSCLC in Australia, Korea, Taiwan and Brazil

	Australia (*N* = 208)			Korea (*N* = 150)			Taiwan (*N* = 217)		Brazil (*N* = 175)		
Characteristic	**SCC**	**NSCC**	**Unk**	**SCC**	**NSCC**	**Unk**	**SCC**	**NSCC**	**SCC**	**NSCC**	**Unk**
Histology, *n* (%)	30 (14)	161 (77)	17 (8)	30 (20)	113 (75)	7 (5)	16 (7)	201 (93)	35 (20)	132 (75)	8 (5)
Male patients, *n* (%)	24 (80)	90 (56)	11 (65)	28 (93)	71 (63)	5 (71)	13 (81)	90 (45)	26 (74)	83 (63)	6 (75)
Age, mean (*SD*), years	64.1 (9.3)	63.3 (10.2)	64.2 (11.8)	64.7 (9.1)	61.2 (10.2)	62.7 (14.1)	65.7 (12.4)	64.4 (12.3)	64.9 (8.8)	62.8 (10.5)	62.1 (9.4)
Age range, years	46–82	37–89	39–83	41–79	31–82	44–83	38–79	30–92	35–81	41–85	48–75
Race, *n* (%)											
Caucasian	19 (63)	124 (77)	6 (35)	0	0	0	0	0	17 (49)	56 (42)	4 (50)
Asian	4 (13)	11 (7)	1 (6)	30 (100)	113 (100)	7 (100)	16 (100)	200 (100)	0	1 (1)	0
Black	0	1 (1)	0	0	0	0	0	1 (1)	2 (6)	6 (5)	1 (13)
Other	1 (3)	11 (7)	0	0	0	0	0	0	0	1 (1)	0
Unknown	6 (20)	14 (9)	10 (59)	0	0	0	0	0 (0)	16 (46)	68 (52)	3 (38)
BMI categories, *n* (%)[a]											
Underweight	0	6 (4)	2 (12)	1 (3)	12 (11)	2 (29)	4 (25)	13 (7)	3 (9)	11 (8)	1 (13)
Normal	17 (57)	76 (47)	7 (41)	24 (80)	77 (68)	4 (57)	7 (4)	132 (66)	19 (54)	56 (42)	6 (75)
Overweight	8 (27)	55 (34)	5 (29)	5 (17)	18 (16)	1 (14)	3 (19)	46 (23)	9 (26)	38 (29)	1 (13)
Obese	4 (13)	22 (14)	3 (18)	0	6 (5)	0	0	8 (4)	3 (9)	20 (15)	0
Unknown	1 (3)	2 (1)	0	0	0	0	0	2 (1)	1 (3)	7 (5)	0
History of smoking, *n* (%)											
Current	10 (33)	38 (24)	6 (35)	21 (70)	28 (25)	2 (29)	4 (25)	16 (8)	8 (23)	18 (14)	0
Former	18 (60)	98 (61)	9 (53)	6 (20)	36 (32)	2 (29)	6 (37)	45 (22)	24 (69)	80 (61)	6 (75)
Never	2 (7)	22 (14)	1 (6)	3 (10)	45 (40)	3 (43)	5 (31)	138 (69)	3 (9)	31 (24)	1 (13)
Unknown	0	3 (2)	1 (6)	0	4 (4)	0	1 (6)	2 (1)	0	3 (2)	1 (13)
Selected comorbidities, *n* (%)[b]											
COPD	12 (48)	33 (23)	6 (38)	3 (12)	2 (2)	0	2 (14)	15 (8)	4 (12)	14 (13)	0
Cardiovascular disease	6 (24)	24 (17)	4 (25)	0	2 (2)	1 (17)	3 (21)	8 (4)	7 (21)	18 (16)	2 (29)
Diabetes mellitus	6 (24)	17 (12)	2 (13)	5 (20)	19 (20)	1 (17)	2 (14)	39 (20)	6 (18)	19 (17)	2 (29)

The "Unknown" category includes patients for whom data were incomplete or missing. Percentages may not total 100 because of rounding.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; NSCC, non-squamous cell carcinoma; Unk, unknown histology.

[a]BMI categories were defined as follows (in kg/m^2): underweight, ≤18.49; normal, 18.50–24.99; overweight, 25.00–29.99; obese, ≥30.00.

[b]Comorbidities are reported for patients with non-missing data, including a total of 184, 128, 209 and 152 in Australia, Korea, Taiwan and Brazil respectively.

2006). Therefore, it is important to understand the use of NSCLC therapies and outcomes in real-world clinical practice.

The PIvOTAL study (Global treatment **P**atterns, resource utilisation and b**IO**marker **T**esting of **A**dvanced non-small cell **L**ung cancer) was a multinational retrospective cohort study conducted at academic and community oncology centres in nine countries in Europe, Asia, Australia, and North and South America from January 2011 with follow-up into May 2016. The primary study objective was to describe contemporary treatment patterns for patients with a confirmed diagnosis of locally advanced/metastatic (stage IIIB/IV) NSCLC who received first-line therapy. In addition, we aimed to describe biopsy (tissue sampling) and NSCLC-related predictive biomarker testing practice patterns and to assess overall survival (OS) from start of first- and second-line therapy. This article reports our findings from Italy, Spain, Germany, Australia, Korea, Taiwan and Brazil. Findings from Japan are reported in a separate publication (Kato et al., 2016).

2 | METHODS

2.1 | Study design and patients

This observational, non-interventional study drew on de-identified patient data abstracted from medical records at academic and community oncology clinics. Study centres were identified in each country based on positive responses to a site qualification questionnaire indicating an interest in study participation, as well as experience in managing patients with NSCLC, availability of biomarker testing and adequate resources to support participation in the study.

Adult patients (≥18 years of age) who presented with newly diagnosed stage IIIB or stage IV NSCLC from January 1, 2011, to July 1, 2013 (to July 1, 2014, in Germany), and who initiated first-line systemic anticancer therapy, were eligible for the study. Histological and/or cytological confirmation of stage IIIB or stage IV NSCLC was an eligibility criterion, with staging done according to the latest TNM classification (Edge et al., 2010; Sobin, Gospodarowicz, & Wittekind, 2009). In addition, eligible patients were required to have complete medical records from the date of diagnosis to the end of the study period (or death, if earlier). Patients who did not receive systemic therapy for NSCLC were excluded, as were those with an initial diagnosis of an early stage NSCLC (stage I to IIIA) who progressed to stage IIIB or IV. Other exclusion criteria were a concomitant or prior history of malignancy and participation in any cancer-related clinical trial.

Eligible patients were identified via medical records at each participating centre. The selection of eligible patients began from the end of the eligibility period, working backwards in time within that period until suitable numbers of patients were reached for each centre. The date of initiation of first-line therapy for each patient after confirmation of the diagnosis was defined as their *index date*. Patients were followed from the index date until the record abstraction date (in 2015–2016), defined as the first site initiation in each country, or until death, whichever occurred first.

The study protocol was approved by the appropriate institutional review board or independent ethics committee for each study site. Informed consent was collected for patients from Italy, Spain, Germany and Brazil who were alive at the time of chart abstraction. Informed consent was not required for working with de-identified retrospective data in the other countries.

2.2 | Data collection and outcomes

Each patient's medical record was given a unique number, and all identifiable patient data were restricted to the site and treating physician. Electronic case report forms were used to abstract de-identified data from the medical records regarding patient demographic characteristics, smoking status and other disease-related variables, predictive biomarker testing and biopsy practices, treatments administered and other health care resource use. We captured the frequency and results of testing for sensitising mutations in the epidermal growth factor receptor (*EGFR*) gene and for anaplastic lymphoma kinase (*ALK*) gene rearrangements. The primary investigator for each site confirmed all data entry and performed all assessments requiring medical opinion, for example, identifying the date of progression after treatment and deciding whether a dose delay, omission of a dose or utilisation of a health care resource occurred secondary to a treatment-related adverse event.

As part of the protocol, investigators were provided with NSCLC staging guidelines according to the TNM classification (Edge et al., 2010; Sobin et al., 2009) and with treatment response criteria based on the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) (Eisenhauer et al., 2009). Performance status on the index date was assessed using the Eastern Cooperative Oncology Group (ECOG) score (Oken et al., 1982) or the Karnofsky scale (Buccheri, Ferrigno, & Tamburini, 1996). The duration of treatment in each line of systemic therapy was calculated in days as [the stop date of treatment line—start date of treatment line +1 day].

Because this was a retrospective study, all patients were assessed and treated according to the usual practice of the treating physician.

2.3 | Statistical analyses

Data from medical records were analysed descriptively and reported using summary statistics by country. Overall survival (OS) from initiation of first- and second-line therapy, by histological classification and by treatment regimen, 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. The inclusion of approximately 150–200 patients per country in the first-line setting was planned on the basis of precision estimates and attrition rates around the primary objective. Prior real-world studies have reported that approximately 39% of patients who receive first-line therapy will receive second-line therapy (Bischoff et al., 2010; Gerber et al., 2011; Vergnenegre et al., 2012), and 22% of patients who receive second-line therapy will receive third-line therapy (Pan, Mallick, Dhanda, & Nadler, 2013).

All analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Patients

Medical records were abstracted from three to 13 study centres in each of the seven countries. All study sites in Australia and Taiwan were centres affiliated with an academic institution; in the other countries, study sites were a mix of academic and community oncology clinics (details in Table S1). Index dates (dates of first-line therapy initiation) ranged from January 19, 2011, to July 1, 2014, and record abstraction dates ranged from April 24, 2015, in Australia to May 27, 2016, in Brazil (Table S1).

The study population of 1265 patients included from 139 patients (Germany) to 217 patients (Taiwan) in each country. The distribution of squamous and non-squamous NSCLC was similar among the countries, with approximately three-quarters being of non-squamous histology, except in Taiwan (93%). The proportion of patients with unknown histology was more variable, with 2%–8% in most countries except Spain (14%) and Taiwan (none; Tables 1 and 2). Patients in the squamous cohorts tended to be slightly older on average, as well as more likely to be male and current or ex-smokers, than those in the non-squamous cohorts. From 4% (Korea) to 33% (Germany) of patients had concomitant chronic obstructive pulmonary disease (COPD). In Taiwan, patients with non-squamous carcinoma were predominantly female (55%) and never-smokers (69%), both higher percentages compared with other countries (Tables 1 and 2).

3.2 | NSCLC-related characteristics

The majority of patients presented with Stage IV NSCLC (78% to 93% by country), with the highest proportions in the non-squamous cohorts (Tables 3 and 4). The diagnosis was made most commonly by biopsy or by both biopsy and cytology; however, the diagnosis relied on cytology for a substantial percentage of patients in Australia (33%) and Spain (31%). The most common locations of metastases are summarised according to histology, by country, in Tables S2 and S3. The proportion of patients who had brain metastases in each country was from 13% (Germany) to 27% (Korea).

The Eastern Cooperative Oncology Group (ECOG) performance status at the index date was available for three-quarters or more of patients in all countries except Italy (57%), Spain (64%) and Korea (45%). Of the patients with a recorded ECOG PS, over 70% in each country had a score of 0–1, ranging from 71% of patients in Spain to 96% in Germany (Tables 3 and 4).

TABLE 3 NSCLC-related characteristics of patients with advanced NSCLC in Italy, Spain and Germany

	Italy (*N* = 174)			Spain (*N* = 202)			Germany (*N* = 139)		
Characteristic	SCC *N* = 42	NSCC *N* = 121	Unk *N* = 11	SCC *N* = 33	NSCC *N* = 140	Unk *N* = 29	SCC *N* = 28	NSCC *N* = 108	Unk *N* = 3
Stage at diagnosis, *n* (%)									
IIIB	5 (12)	7 (6)	1 (9)	10 (30)	6 (4)	1 (3)	11 (39)	19 (18)	1 (33)
IV	37 (88)	114 (94)	10 (91)	23 (70)	134 (96)	28 (97)	17 (61)	89 (82)	2 (67)
Basis of diagnosis, *n* (%)									
Biopsy sample	31 (74)	89 (74)	10 (91)	16 (49)	70 (50)	12 (41)	20 (71)	68 (63)	3 (100)
Cytology sample	1 (2)	24 (20)	1 (9)	6 (18)	44 (31)	12 (41)	2 (7)	5 (5)	0
Both biopsy and cytology	10 (24)	8 (7)	0	11 (33)	26 (19)	5 (17)	6 (21)	35 (32)	0
Tested for biomarker(s), *n* (%)	1 (2)	79 (65)	9 (82)	14 (42)	119 (85)	21 (72)	6 (21)	71 (66)	1 (33)
Tested for *EGFR* mutation, *n* (%)	1 (2)	76 (63)	9 (82)	12 (36)	109 (78)	20 (69)	5 (18)	65 (60)	1 (33)
EGFR-positive, *n* (% of tested)[a]	0	18 (24)	4 (44)	0	18 (17)	4 (20)	1 (20)	18 (28)	0
Tested for *ALK* rearrangement, *n* (%)	1 (2)	30 (25)	2 (18)	4 (12)	39 (28)	2 (7)	4 (14)	39 (36)	1 (33)
ALK-positive, *n* (% of tested)[a]	0	1 (3)	0	0	2 (5)	1 (50)	0	2 (5)	0
ECOG PS at index date, *n* (%)									
0–1	17 (77)	65 (92)	5 (83)	14 (64)	64 (72)	13 (72)	16 (94)	81 (96)	2 (100)
2–3	5 (23)	6 (8)	1 (17)	8 (36)	23 (26)	5 (28)	1 (6)	3 (4)	0
4	0	0	0	0	2 (2)	0	0	0	0
Unknown, *n*	20	50	5	11	51	11	11	24	1
Treatment before index, *n* (%)									
Surgery alone	3 (7)	21 (17)	0	1 (3)	1 (1)	1 (3)	0	8 (7)	0
Radiotherapy alone	8 (19)	17 (14)	1 (9)	14 (41)	40 (29)	9 (31)	8 (29)	23 (21)	1 (33)
Surgery plus radiotherapy	1 (2)	1 (1)	0	1 (3)	5 (4)	1 (3)	1 (4)	3 (3)	0

The "Unknown" category includes patients for whom data were incomplete or missing. Percentages may not total 100 because of rounding.
ALK, anaplastic lymphoma kinase gene; ECOG PS, Eastern Cooperative Study Group performance status; *EGFR*, epidermal growth factor receptor gene; index, date of initiation of first-line therapy for NSCLC; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; NSCC, non-squamous cell carcinoma; Unk, unknown histology.
[a]Results for the other patients tested were mostly negative, and a small minority were inconclusive or unknown.

3.3 | Molecular testing for predictive biomarkers

In the non-squamous cohorts, biomarker testing was done for the majority of patients, ranging from 54% in Brazil to 91% in Taiwan (Tables 3 and 4). Testing for *EGFR* mutation was done most frequently (varying from 52% of the non-squamous cohort in Brazil to 91% in Taiwan), while the percentage of patients who were tested for *ALK* rearrangement was lowest in Taiwan (2.5%) and highest in Korea (47%) for non-squamous NSCLC. The percentage of patients with *EGFR*-positive non-squamous NSCLC was lowest in Brazil, Australia and the European countries (17% to 28%) and highest in Korea and Taiwan (40% and 68%, respectively). Few patients with non-squamous NSCLC had *ALK*-positive tumours (Tables 3 and 4).

In the squamous cohorts, less than a quarter of patients in each country were tested for biomarkers except in Spain (42%). From 0 to two patients with squamous NSCLC in each country had *EGFR*-positive tumours; none had *ALK*-positive tumours (Tables 3 and 4).

3.4 | Systemic therapy for NSCLC

After receiving first-line therapy in accordance with study enrolment criteria, from 46% (Germany) to 71% (Taiwan) of patients in each country received second-line therapy and then 17% (Brazil) to 42% (Taiwan) received third-line therapy. The most common first-, second- and third-line regimens administered in each country are outlined according to regimen category in Tables 5 and 6 together with number of cycles administered and treatment duration. Treatment regimens are further detailed, by histology, in Tables S4–S7.

Platinum-based regimens were the most common first-line therapy in every country except in Taiwan, where EGFR tyrosine kinase inhibitors (TKIs), particularly gefitinib, were the most common first-line therapy. Carboplatin and cisplatin were administered in roughly equal proportions in most countries except in Australia and Brazil, where carboplatin-based regimens predominated (Tables 5 and 6).

TABLE 4 NSCLC-related characteristics of patients with advanced NSCLC in Australia, Korea, Taiwan and Brazil

	Australia (*N* = 208)			Korea (*N* = 150)			Taiwan (*N* = 217)		Brazil (*N* = 175)		
Characteristic	SCC *N* = 30	NSCC *N* = 161	Unk *N* = 17	SCC *N* = 30	NSCC *N* = 113	Unk *N* = 7	SCC *N* = 16	NSCC *N* = 201	SCC *N* = 35	NSCC *N* = 132	Unk *N* = 8
Stage at diagnosis, *n* (%)											
IIIB	12 (40)	31 (19)	1 (6)	14 (47)	12 (11)	0	4 (25)	16 (8)	4 (11)	13 (10)	1 (13)
IV	18 (60)	130 (81)	16 (94)	16 (53)	101 (89)	7 (100)	12 (75)	185 (92)	31 (89)	119 (90)	7 (88)
Basis of diagnosis, *n* (%)											
Biopsy sample	15 (50)	79 (49)	10 (59)	20 (67)	67 (59)	4 (57)	11 (69)	123 (61)	33 (94)	110 (83)	6 (75)
Cytology sample	8 (27)	57 (35)	4 (24)	0	14 (12)	1 (14)	1 (6)	41 (20)	2 (6)	18 (14)	2 (25)
Both biopsy and cytology	7 (23)	25 (16)	3 (18)	10 (33)	32 (28)	2 (29)	4 (25)	37 (18)	0	4 (3)	0
Tested for biomarker(s), *n* (%)	3 (10)	115 (71)	8 (47)	7 (23)	101 (89)	6 (86)	2 (13)	183 (91)	2 (6)	71 (54)	2 (25)
Tested for *EGFR* mutation, *n* (%)	3 (10)	113 (70)	7 (41)	5 (17)	98 (87)	5 (71)	2 (13)	182 (91)	2 (6)	69 (52)	2 (25)
EGFR-positive, *n* (% of tested)[a]	2 (67)	25 (22)	0	1 (20)	39 (40)	4 (80)	0	123 (68)	0	12 (17)	1 (50)
Tested for *ALK* rearrangement, *n* (%)	1 (3)	25 (16)	1 (6)	2 (7)	53 (47)	2 (29)	0	5 (2)	0	14 (11)	0
ALK-positive, *n* (% of tested)[a]	0	4 (16)	0	0	9 (17)	0	0	3 (60)	0	0	0
ECOG PS at index date, *n* (%)[b]											
0–1	19 (90)	109 (90)	10 (91)	12 (92)	46 (88)	3 (100)	11 (69)	149 (79)	13 (65)	78 (74)	5 (83)
2–3	2 (10)	11 (9)	1 (9)	1 (8)	6 (12)	0	5 (31))	36 (19)	7 (35)	28 (26)	1 (17)
4	0	1 (1)	0	0	0	0	0	4 (2)	0	0	0
Unknown, *n*	9	40	6	17	61	4	0	12	15	26	2
Treatment before index, *n* (%)											
Surgery alone	0	16 (10)	0	1 (3)	1 (1)	2 (29)	2 (13)	15 (8)	1 (3)	8 (6)	0
Radiotherapy alone	8 (27)	48 (30)	5 (29)	8 (27)	36 (32)	1 (14)	3 (19)	39 (19)	3 (9)	19 (14)	2 (25)
Surgery plus radiotherapy	1 (3)	14 (9)	0	1 (3)	3 (3)	0	1 (2)	7 (4)	0	6 (5)	0

The "Unknown" category includes patients for whom data were incomplete or missing. Percentages may not total 100 because of rounding.

ALK, anaplastic lymphoma kinase gene; ECOG PS, Eastern Cooperative Study Group performance status; *EGFR*, epidermal growth factor receptor gene; index, date of initiation of first-line therapy for NSCLC; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; NSCC, non-squamous cell carcinoma; Unk, unknown histology.

[a]Results for the other patients tested were mostly negative, and a small minority were inconclusive or unknown.

TABLE 5 Treatment patterns for first-, second- and third-line therapy, by histology, in Italy, Spain and Germany

	Italy (*N* = 174)			Spain (*N* = 202)			Germany (*N* = 139)		
Systemic therapy[a]	SCC *N* = 42	NSCC *N* = 121	Unk *N* = 11	SCC *N* = 33	NSCC *N* = 140	Unk *N* = 29	SCC *N* = 28	NSCC *N* = 108	Unk *N* = 3
First-line therapy[b]	42 (100)	121 (100)	11 (100)	33 (100)	140 (100)	29 (100)	28 (100)	108 (100)	3 (100)
Platinum-based combination	31 (74)	101 (84)	8 (73)	29 (88)	122 (87)	25 (86)	28 (100)	91 (84)	3 (100)
Carboplatin-based	16 (38)	48 (40)	7 (64)	10 (29)	59 (42)	13 (45)	14 (50)	46 (43)	0
Cisplatin-based	0	6 (5)	1 (9)	18 (53)	61 (43)	12 (42)	14 (50)	42 (39)	3 (100)
Carboplatin and cisplatin	15 (36)	47 (39)	0	1 (3)	2 (1)	0	0	3 (3)	0
Non-platinum combination	0	0	0	0	2 (1.4)	0	0	0	0
Single agent	11 (26)	8 (7)	0	4 (12)	7 (5)	1 (3)	0	11 (10)	0
EGFR/ALK TKI	0	12 (10)	3 (27)	0	9 (6)	3 (10)	0	6 (6)	0
Duration, median (range), days[c]	79 (1–196)	112 (1–871)	141 (9–632)	87 (1–641)	137 (1–927)	96 (1–304)	108 (32–643)	99 (1–853)	274 (92–575)
Duration, mean (*SD*), days	76 (49)	141 (136)	200 (188)	109 (120)	187 (175)	111 (77)	128 (118)	170 (181)	314 (244)
Available cycle data, *n*	41	118	11	33	139	29	28	107	3
No. completed cycles, median (range)	4 (1–6)	5 (1–16)	6 (1–21)	4 (0–12)	4 (1–20)	4 (1–12)	4 (1–8)	4 (1–21)	4 (4–4)
1–3 cycles	19 (45)	43 (36)	3 (27)	14 (42)	37 (26)	9 (31)	5 (18)	34 (31)	0
4–6 cycles	22 (52)	61 (50)	4 (36)	15 (46)	83 (59)	15 (52)	22 (84)	68 (64)	3 (100)
>6 cycles	0	14 (12)	4 (36)	4 (12)	19 (14)	5 (17)	1 (3.4)	5 (5)	0
Cycle length, median (range) days	19 (1–33)	19 (0–201)	29 (9–31)	18 (1–66)	19 (1–260)	18 (0–31)	20 (10–38)	20 (1–93)	23 (21–23)
Mean (*SD*)	18 (8)	21 (18)	25 (7)	21 (11)	23 (14)	18 (7)	22 (7)	22 (12)	22 (1)
Second-line therapy, *n* (%)	19 (45)	75 (62)	6 (55)	12 (36)	70 (50)	10 (34)	17 (59)	45 (42)	1 (33)
Platinum-based combination	2 (10.5)	9 (12.0)	2 (33.3)	2 (16.7)	18 (25.7)	2 (20.0)	7 (41)	13 (29)	0
Carboplatin-based	1 (5)	7 (9)	2 (33)	1 (8)	14 (20)	1 (10)	5 (29)	9 (20)	0
Cisplatin-based	1 (5)	2 (3)	0	1 (8)	4 (6)	1 (10)	2 (12)	4 (9)	0
Carboplatin and cisplatin	0	0	0	0	0	0	0	0	0
Non-platinum combination	0	0	0	4 (33)	4 (6)	1 (10)	0	5 (11)	0
Single agent	15 (79)	37 (49)	1 (17)	3 (25)	30 (43)	6 (60)	9 (53)	14 (31)	0
EGFR/ALK TKI	2 (11)	29 (39)	3 (50)	3 (25)	16 (23)	0	1 (6)	13 (29)	0
Other NSCLC anticancer agent	0	0	0	0	2 (3)	1 (10)	0	0	1 (100)
Duration, median (range), days	84 (1–233)	64 (1–638)	111 (43–257)	65 (19–172)	68 (2–342)	43 (1–533)	60 (1–291)	81 (1–535)	123
Duration, mean (*SD*) days	88 (49)	93 (109)	129 (92)	74 (65)	90 (69)	104 (157)	66 (64)	120 (125)	123
Available cycle data, *n*	19	69	6	12	68	10	17	40	1
No. completed cycles, median (range)	4 (1–12)	3 (0–21)	4 (1–7)	3 (2–9)	3 (1–15)	2 (1–17)	2 (1–10)	3 (1–17)	6
1–3 cycles	9 (47)	39(51)	3 (50)	7 (58)	26 (50)	7 (70)	11 (65)	21 (47)	0
4–6 cycles	8 (42)	23 (30)	2 (33)	4 (33)	25 (36)	2 (20)	5 (29)	12 (27)	1 (100)
>6 cycles	2 (11)	7 (9)	1 (17)	1 (8)	8 (11)	1 (10)	1 (6)	7 (16)	0

(Continues)

TABLE 5 (Continued)

Systemic therapy[a]	Italy (*N* = 174)			Spain (*N* = 202)			Germany (*N* = 139)		
	SCC *N* = 42	NSCC *N* = 121	Unk *N* = 11	SCC *N* = 33	NSCC *N* = 140	Unk *N* = 29	SCC *N* = 28	NSCC *N* = 108	Unk *N* = 3
Cycle length, median (range) days	21 (1–40)	21 (1–38)	31 (14–32)	25 (10–33)	21 (1–43)	21 (1–31)	21 (1–50)	25 (1–32)	21
Mean (*SD*)	21 (9)	21 (10)	28 (7)	23 (9)	23 (8)	21 (11)	24 (12)	24 (8)	21
Third-line therapy, *n* (%)	8 (19)	32 (26)	4 (36)	7 (21)	35 (25)	3 (10)	8 (28)	22 (20)	0
Platinum-based combination	0	1 (3)	0	1 (14)	6 (17)	0	1 (13)	7 (32)	0
Carboplatin-based	0	1 (3)	0	0	4 (11)	0	1 (13)	4 (18)	0
Cisplatin-based	0	0	0	1 (14)	2 (6)	0	0	2 (9)	0
Carboplatin and cisplatin	0	0	0	0	0	0	0	1 (5)	0
Non-platinum combination	0	0	0	0	6 (17)	1 (33)	2 (25)	2 (9)	0
Single agent	8 (100)	20 (63)	3 (75)	3 (43)	10 (29)	2 (67)	3 (38)	9 (41)	0
EGFR/ALK TKI	0	10 (31)	1 (25)	3 (43)	13 (37)	0	1 (13)	3 (14)	0
Other NSCLC anticancer agent	0	1 (3)	0	0	0	0	1 (13)	1 (5)	0
Duration, median (range), days	60 (1–95)	77 (1–387)	68 (22–145)	99 (5–197)	71 (1–346)	56 (45–91)	90 (1–427)	190 (22–550)	0
Duration, mean (*SD*) days	53 (32)	91 (74)	76 (51)	93 (80)	74 (64)	64 (24)	135 (138)	202 (158)	0
Available cycle data, *n*	*8*	*31*	*4*	*7*	*34*	*3*	*8*	*19*	*0*
No. completed cycles, median (range)	4 (1–7)	3 (1–13)	3 (2–9)	3 (0–10)	3 (0–15)	3 (3–3)	4 (1–10)	6 (2–14)	0
1–3 cycles	3 (38)	16 (50)	2 (50)	4 (57)	24 (69)	3 (100)	4 (50)	5 (23)	0
4–6 cycles	4 (50)	9 (28)	1 (25)	2 (29)	6 (17)	0	3 (38)	7 (32)	0
>6 cycles	1 (13)	6 (19)	1 (25)	1 (14)	4 (11)	0	1 (12)	7 (32)	0
Cycle length, median (range) days	17 (1–31)	23 (1–43)	17 (11–31)	31 (9–38)	27 (1–35)	19 (15–49)	30 (1–43)	26 (7–36)	0
Mean (*SD*)	16 (9)	23 (10)	19 (9)	26 (10)	23 (9)	28 (19)	26 (13)	25 (8)	0

Data are *n* (%) unless otherwise specified.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NSCC, non-squamous cell carcinoma; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor; Unk, unknown histology.

[a]The five systemic therapy categories were defined as follows:

- Platinum-based combination: regimen with two or more anticancer therapies including carboplatin or cisplatin.
- Non-platinum combination: regimen with two or more anticancer therapies not including carboplatin or cisplatin (can contain bevacizumab in combination with other non-platinum drug).
- Single agent: regimen of one anticancer drug that was not an EGFR or ALK tyrosine kinase inhibitor (TKI).
- EGFR/ALK TKI: monotherapy with anti-EGFR (erlotinib, gefitinib, afatinib) or anti-ALK agent (crizotinib, ceritinib).
- Other NSCLC anticancer agent: any other agent not included in the prior categories, e.g. TS-1 (oral anticancer drug composed of tegafur, gimestat and otastat potassium at a molar ratio of 1:0.4:1).

[b]No patient received an "other NSCLC anticancer agent" in first line.

[c]The duration of treatment (days) in a treatment line was calculated as [stop date of treatment line—start date of treatment line +1 day].

TABLE 6 Treatment patterns for first-, second- and third-line therapy, by histology, in Australia, Korea, Taiwan and Brazil

	Australia (*N* = 208)			Korea (*N* = 150)			Taiwan (*N* = 217)		Brazil (*N* = 175)		
Systemic therapy[a]	SCC *N* = 30	NSCC *N* = 161	Unk *N* = 17	SCC *N* = 30	NSCC *N* = 113	Unk *N* = 7	SCC *N* = 16	NSCC *N* = 201	SCC *N* = 35	NSCC *N* = 132	Unk *N* = 8
First-line therapy[b]	30 (100)	161 (100)	17 (100)	30 (100)	113 (100)	7 (100)	16 (100)	201 (100)	35 (100)	132 (100)	8 (100)
Platinum-based combination	26 (87)	131 (81)	15 (88)	30 (100)	83 (74)	5 (71)	8 (50)	33 (17)	35 (100)	121 (92)	7 (88)
Carboplatin-based	22 (73)	115 (71)	14 (82)	20 (67)	43 (38)	3 (43)	4 (25)	6 (3)	23 (65)	87 (66)	6 (75)
Cisplatin-based	3 (10)	15 (9)	1 (6)	10 (33)	40 (35)	2 (29)	4 (25)	26 (13)	12 (34)	32 (24)	1 (13)
Carboplatin and cisplatin	1 (3)	1 (1)	0	0	0	0	0	1 (1)	0	2 (2)	0
Non-platinum combination	0	0	0	0	1 (1)	1 (14)	3 (19)	25 (12)	0	0	0
Single agent	2 (7)	16 (10)	2 (12)	0	5 (4)	0	5 (31)	32 (16)	0	7 (5)	1 (13)
EGFR/ALK TKI	2 (7)	14 (9)	0	0	24 (21)	1 (14)	0	111 (55)	0	4 (3)	0
Duration, median (range), days[c]	65 (1–413)	68 (1–742)	44 (9–242)	67 (16–153)	68 (1–797)	29 (1–51)	71 (5–594)	214 (1–918)	105 (1–432)	78 (1–643)	57 (22–71)
Duration, mean (*SD*) days	74 (78)	132 (162)	69 (61)	71 (37)	115 (163)	27 (20)	136 (169)	263 (207)	92 (75)	112 (111)	52 (19)
Available cycle data, *n*	30	157	17	30	109	7	16	184	35	132	8
No. completed cycles, median (range)	3 (0–14)	4 (1–17)	3 (1–6)	4 (1–10)	4 (0–21)	2 (0–5)	3 (1, 11)	6 (0–21)	5 (1–6)	4 (0–21)	3 (2–4)
1–3 cycles	15 (50)	67 (42)	9 (47)	9 (30)	48 (43)	6 (57)	10 (63)	49 (24)	13 (37)	41 (31)	8 (63)
4–6 cycles	14 (47)	80 (50)	8 (47)	16 (53)	42 (43)	1 (14)	3 (19)	52 (26)	22 (63)	84 (64)	3 (38)
>6 cycles	1 (3)	10 (6)	0	5 (17)	13 (12)	0	3 (19)	76 (38)	0	7 (5)	0
Cycle length, median (range) days	18 (1–41)	18 (1–291)	16 (5–32)	18 (5–52)	18 (1–199)	17 (1–33)	21 (4–397)	31 (1–597)	19 (1–31)	18 (0–194)	17 (11–19)
Mean (*SD*)	19 (10)	21 (28)	17 (7)	18 (11)	19 (20)	18 (12)	49 (95)	39 (65)	18 (7)	19 (17)	16 (3)
Second-line therapy, *n* (%)	14 (47)	100 (61)	14 (82)	19 (63)	74 (65)	3 (43)	13 (81)	142 (71)	16 (46)	71 (54)	4 (50)
Platinum-based combination	2 (14)	19 (19)	1 (7)	1 (5)	10 (14)	0	3 (23)	44 (31)	1 (6)	13 (18)	0
Carboplatin-based	2 (14)	19 (19)	1 (7)	0	9 (12)	0	1 (8)	8 (6)	0	8 (11)	0
Cisplatin-based	0	0	0	1 (5)	1 (1)	0	2 (15)	34 (24)	1 (6)	5 (7)	0
Carboplatin and cisplatin	0	0	0	0	0	0	0	2 (1)	0	0	0
Non-platinum combination	0	0	1 (7)	3 (16)	0	0	3 (23)	27 (19)	0	1 (1)	1 (25)
Single agent	9 (64)	60 (60)	8 (57)	7 (37)	24 (32)	1 (33)	6 (46)	44 (31)	14 (88)	51 (72)	3 (75)
EGFR/ALK TKI	3 (21)	21 (21)	4 (29)	8 (42)	40 (54)	2 (67)	1 (8)	27 (19)	1 (6)	6 (9)	0
Duration, median (range), days	29 (5–113)	71 (1–664)	43 (1–407)	49 (1–760)	48 (1–520)	15 (8–230)	92 (15–189)	134 (1–827)	38 (1–140)	57 (1–497)	85 (23–655)
Duration, mean (*SD*) days	44 (34)	120 (137)	97 (127)	83 (168)	110 (132)	84 (126)	96 (59)	175 (177)	52 (42)	80 (87)	212 (300)
Available cycle data, *n*	14	97	14	19	72	3	13	136	16	70	4
No. completed cycles, median (range)	2 (1–6)	4 (1–24)	3 (0–13)	2 (0–25)	3 (0–23)	1 (0–8)	3 (1, 6)	4 (0–25)	3 (1–6)	3 (1–17)	4 (2–11)
1–3 cycles	12 (86)	48 (48)	8 (57)	15 (79)	46 (62)	2 (67)	7 (54)	61 (43)	11 (69)	46 (65)	2 (50)

(Continues)

TABLE 6 (Continued)

Systemic therapy[a]	Australia (*N* = 208)			Korea (*N* = 150)			Taiwan (*N* = 217)		Brazil (*N* = 175)		
	SCC *N* = 30	NSCC *N* = 161	Unk *N* = 17	SCC *N* = 30	NSCC *N* = 113	Unk *N* = 7	SCC *N* = 16	NSCC *N* = 201	SCC *N* = 35	NSCC *N* = 132	Unk *N* = 8
4–6 cycles	2 (14)	28 (28)	3 (21)	3 (16)	9 (12)	0	6 (46)	36 (25)	5 (31)	18 (25)	1 (25)
>6 cycles	0	21 (21)	3 (21)	1 (5)	17 (23)	1 (33)	0	32 (23)	0	6 (9)	1 (25)
Cycle length, median (range) days	18 (5–32)	19 (1–54)	19 (1–33)	25 (1–46)	31 (1–33)	31 (8–33)	27 (7–89)	4 (0–25)	18 (1–31)	19 (1–138)	19 (12–60)
Mean (*SD*)	18 (10)	21 (9)	18 (12)	23 (12)	24 (10)	24 (14)	29 (20)	5 (5.5)	17 (8)	21 (18)	27 (22)
Third-line therapy, *n* (%)	4 (13)	40 (25)	8 (47)	10 (23)	46 (41)	3 (43)	7 (44)	84 (42)	6 (17)	22 (17)	2 (25)
Platinum-based combination	1 (25)	6 (15)	1 (13)	1 (10)	3 (7)	0	1 (14)	2 (2)	1 (17)	3 (14)	0
Carboplatin-based	1 (25)	6 (15)	1 (13)	0	2 (4)	0	0	0	1 (17)	3 (14)	0
Cisplatin-based	0	0	0	1 (10)	1 (2)	0	1 (14)	2 (2)	0	0	0
Carboplatin and cisplatin	0	0	0	0	0	0	0	0	0	0	0
Non-platinum combination	1 (25)	3 (8)	0	1 (10)	3 (7)	0	0	13 (16)	0	3 (14)	0
Single agent	1 (25)	14 (35)	2 (25)	4 (40)	28 (61)	2 (67)	2 (29)	24 (29)	4 (67)	9 (41)	2 (100)
EGFR/ALK TKI	1 (25)	13 (33)	5 (63)	4 (40)	12 (26)	1 (33)	4 (57)	44 (52)	1 (17)	7 (32)	0
Other NSCLC anticancer agent	0	4 (10)	0	0	0	0	0	1 (1)	0	0	0
Duration, median (range), days	110 (8–145)	85 (8–752)	78 (22–269)	24 (5–56)	35 (1–602)	19 (4–209)	34 (12–109)	82 (1–736)	67 (21–210)	93 (7–254)	50 (22–78)
Duration, mean (*SD*) days	94 (60)	133 (145)	91 (87)	27 (20)	80 (127)	77 (114)	47 (35)	126 (133)	85 (72)	102 (61)	50 (40)
Available cycle data, *n*	4	38	7	10	43	3	7	80	6	18	2
No. completed cycles, median (range)	4 (1–6)	3 (1–14)	3 (1–9)	1 (0–3)	2 (0–14)	2 (0–8)	1 (0–4)	2 (0–16)	3 (1–7)	4 (0–11)	3 (2–4)
1–3 cycles	2 (50)	22 (55)	4 (50)	10 (100)	31 (67)	2 (67)	5 (72)	47 (56)	4 (67)	8 (36)	1 (50)
4–6 cycles	3 (50)	10 (25)	2 (25)	0	7 (15)	0	1 (14)	17 (20)	1 (17)	6 (27)	1 (50)
>6 cycles	0	6 (15)	1 (13)	0	5 (11)	1 (33)	0	12 (14)	1 (17)	4 (18)	0
Cycle length, median (range) days	24 (8–31)	31 (8–33)	31 (11–32)	22 (8–38)	17 (1–39)	26 (10–41)	31 (7–109)	31 (1–379)	25 (13–31)	23(15–42)	15 (11–20)
Mean (*SD*)	22 (11)	25 (8)	24 (9)	22 (11)	17 (11)	25 (16)	37 (33)	40 (51)	23 (8)	25 (7)	15 (6)

Data are *n* (% of non-missing) unless otherwise specified.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NSCC, non-squamous cell carcinoma; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor; Unk, unknown histology.

[a]The five systemic therapy categories were defined as follows:

- Platinum-based combination: regimen with two or more anticancer therapies including carboplatin or cisplatin.
- Non-platinum combination: regimen with two or more anticancer therapies not including carboplatin or cisplatin (can contain bevacizumab in combination with other non-platinum drug).
- Single agent: regimen of one anticancer drug that was not an EGFR or ALK tyrosine kinase inhibitor (TKI).
- EGFR/ALK TKI: monotherapy with anti-EGFR (erlotinib, gefitinib, afatinib) or anti-ALK agent (crizotinib, ceritinib).
- Other NSCLC anticancer agent: any other agent not included in the prior categories, e.g. TS-1 (oral anticancer drug composed of tegafur, gimestat and otastat potassium at a molar ratio of 1:0.4:1).

[b]No patient received an "other NSCLC anticancer agent" in first-line, and only 1 (0.9%) patient in the Taiwan non-squamous cohort received an "other agent" in second line.

[c]The duration of treatment (days) in a treatment line was calculated as [stop date of treatment line—start date of treatment line +1 day].

From 7% (Korea) to 32% (Spain) of patients received maintenance therapy. Table S8 summarises the numbers of patients who received continuation and switch maintenance therapy.

For second-line therapy, single agents were commonly administered, particularly in Brazil and Australia. Otherwise, the treatment patterns varied amongst the countries and according to histologies (Tables 5 and 6). Similarly, for third-line therapy, treatment patterns were varied, and single agents were common in Brazil, as well as in Italy and Korea (details in Tables S4–S7).

3.5 | Overall survival

The median OS from initiation of first-line therapy ranged from 9.3 months in Brazil to 25.5 months in Taiwan (Table 7; Figure 1). In Italy, Australia and Taiwan, patients in the non-squamous cohorts had markedly longer median OS than those in the squamous cohorts, whereas median OS was similar for the two histological subtypes in the other countries (per protocol, OS was not calculated for German patients).

The median OS from initiation of second-line therapy was also shortest in Brazil (5.4 months) and longest in Taiwan (15.8 months). In all countries except Brazil, median OS from initiation of second-line therapy was longer for patients with non-squamous NSCLC than for those with squamous cell carcinoma (Table 7).

4 | DISCUSSION

This multinational retrospective study found both strong similarities as well as wide variation among countries in different aspects of the presentation and management of NSCLC. Similarities among countries included the majority of patients presenting with stage IV disease (78% to 93%), the proportions of patients with squamous versus non-squamous NSCLC (about 20% vs. 75%), and the associated patient demographic characteristics, with the obvious exception of race, which was almost exclusively Caucasian in the European countries, exclusively Asian in Korea and Taiwan, and mixed in Australia and Brazil. The proportion of patients with non-squamous NSCLC who were tested for activating *EGFR* mutation and/or *ALK* rearrangement (54% in Brazil to 91% in Taiwan), and those with positive results, varied widely among countries. Platinum-based regimens were administered most commonly as first-line therapy in all countries except in Taiwan, where the EGFR TKI gefitinib was the most common first-line agent, reflecting the high proportion of patients with non-squamous NSCLC testing positive for *EGFR* mutation (68%). Approximately one-half of patients in each country except Taiwan received second-line therapy (71% in Taiwan), and approximately one-quarter received third-line therapy (39% in Korea and 42% in Taiwan). Taiwan also differed from the other countries with regard to demographic characteristics of the non-squamous cohort, which included >50% women and never-smokers, and higher rates of *EGFR* mutation testing but lower rates of *ALK* rearrangement testing.

The NSCLC diagnostic and treatment patterns recorded in this study were largely in line with guideline recommendations during the study years. Consensus European guidelines at the time of our study eligibility period (2011 to mid-2014) recommended the histological sub-classification of NSCLC, together with *EGFR* testing and, beginning in 2012, *ALK* testing, for patients with non-squamous NSCLC and for light or never-smokers with squamous NSCLC (Besse et al., 2014; Felip, Gridelli, Baas, Rosell, & Stahel, 2011; Kerr et al., 2014; Peters et al., 2012). For first-line therapy of metastatic NSCLC, guidelines recommended platinum-based chemotherapy, four to six cycles; while, for patients with *EGFR*-positive tumours, the recommendation was for an EGFR TKI as first-line therapy or as maintenance therapy, if not received as first line.

Our findings update and expand on findings of prior multinational and single-country observational (non-interventional) studies of NSCLC treatment patterns. In Europe, the reported rate of *EGFR* mutation testing for patients with advanced NSCLC increased over the years from 3.5% in 2006–2008 (Moro-Sibilot et al., 2010), to 26% in 2009–2011 (Schnabel et al., 2012), and then to 50%–70% in the European countries in our study and others in Europe during the same time (2011–2014) (Gridelli et al., 2014). Similarly, in Korea, our study shows increased use of biomarker testing, as compared with retrospective studies looking at earlier years, which reported ~40% of patients tested for *EGFR* mutation during the period from 2007 to 2010 (Choi et al., 2013; Sun et al., 2013).

Differences in national NSCLC drug approval timelines and reimbursement policies could explain some of the differences in predictive biomarker testing rates and treatment patterns among the countries in our study. For example, the EGFR TKIs erlotinib and gefitinib along with their companion diagnostics were approved and reimbursed in European countries and Australia between 2009 and 2013. By contrast, in Brazil, *EGFR* mutation testing was first covered by insurance companies in January 2012, and, as of this writing, is still not covered for patients treated in the public health system. Similarly, *ALK* translocation testing and *ALK* TKIs are not reimbursed in Brazil. Indeed, overall biomarker testing rates for non-squamous NSCLC in Brazil were relatively low in the present study as compared with those in Europe and Australia (54% vs. 65%–71%, respectively). The proportions of patients with *EGFR*-positive non-squamous NSCLC in the five non-Asian countries ranged from 17% in Spain and Brazil to 28% in Germany.

In Korea and Taiwan, the percentages of patients with *EGFR*-positive non-squamous NSCLC were relatively higher, 40% and 68% respectively. This is an expected finding, as the reported prevalence of *EGFR* mutations in lung adenocarcinoma, for example, is much higher in Asia-Pacific populations, averaging 47%, than in European populations (average, 15%) (Midha, Dearden, & Mccormack, 2015). Moreover, the prevalence of *EGFR* mutations in lung adenocarcinoma is higher in women than men and in never-smokers than ever-smokers, which could explain the high prevalence in Taiwan, where the non-squamous cohort included 69% never-smokers and 55% women.

We found a low frequency of testing for *ALK* rearrangements for non-squamous NSCLC in Taiwan (2.5%) as compared with Korea (47%), likely explained by reimbursement policies and the timeline of regulatory approval of anti-ALK agents in those two countries. In Korea, the first ALK inhibitor, crizotinib, was approved in late 2011, and ALK testing was approved in January of 2013. Instead, in Taiwan, ALK testing

TABLE 7 Overall survival (OS) after initiation of first- and second-line therapy for advanced NSCLC[a]

Characteristic	Italy *N* = 174	Spain *N* = 202	Australia *N* = 208	Korea *N* = 150	Taiwan *N* = 217	Brazil *N* = 175
Median OS (95% CI) from start of 1L, months						
Overall	16.7 (12.6–26.2)	10.7 (8.8–12.9)	11.6 (9.2–14.6)	12.0 (9.4–14.1)	25.5 (22.6–31.3)	9.3 (7.6–11.5)
Squamous NSCLC	14.8 (7.0–NR)[b]	10.2 (6.1–15.0)	7.0 (4.3–12.2)	12.1 (7.8–14.1)	9.9 (4.4–26.1)	10.5 (6.9–19.8)
Non-squamous NSCLC	19.7 (13.1–31.9)	12.3 (8.9–14.3)	13.5 (10.6–15.6)	12.0 (9.4–17.5)	26.7 (23.1–32.3)	9.4 (7.3–11.6)
Unknown	10.7 (3.6–22.8)	10.2 (6.7–12.6)	6.9 (4.2–14.7)	3.1 (1.7–20.5)	NA	5.9 (2.0–NR)
Median OS (95% CI) from start of 2L, months						
Overall	12.8 (7.4–25.7)	6.5 (5.2–8.0)	8.0 (6.2–10.8)	6.0 (4.3–8.8)	15.8 (10.5–21.8)	5.4 (4.3–6.2)
Squamous NSCLC	NA (4.7–NR)	4.3 (2.8–14.2)	3.5 (0.9–5.9)	3.4 (1.7–5.7)	6.5 (2.9–11.2)	6.2 (1.9–11.9)
Non-squamous NSCLC	16.6 (7.7–26.4)	6.5 (5.2–8.0)	9.2 (6.6–1.0)	7.2 (4.8–11.4)	16.0 (10.7–22.5)	5.3 (4.0–6.0)
Unknown	6.7 (4.0–NR)	7.1 (1.5–20.8)	6.7 (2.1–13.0)	8.6 (0.8–16.1)	NA	NA (1.8–NR)

1L, first-line therapy; 2L, second-line therapy; 95% CI, 95% confidence interval; NA, not applicable/not available; NR, not reached; OS, overall survival.
[a]OS data for Germany were not specified by the protocol, hence are not available.
[b]The upper bounds of several 95% CIs were not reached because of low patient numbers in some cohorts.

is not subject to regulatory approval (and is not reimbursed), and drug reimbursement is based on approved indication(s). The regulatory approval of crizotinib for second-line therapy for *ALK*-positive NSCLC did not occur until after our study (September 2015); and no other ALK inhibitors were approved in Taiwan during the study. In Taiwan, of the five non-squamous tumours tested, three (60%) were *ALK*-positive; in Korea, the percentage was 17%. By contrast, in the European countries, one-quarter to one-third of non-squamous tumours were tested for *ALK* rearrangement, and 3%–5% were *ALK*-positive.

Routine molecular testing of squamous NSCLC was not recommended by guidelines (Felip et al., 2011; Kerr et al., 2014; Peters et al., 2012); however, we found that predictive biomarker testing was done for one-fifth to almost one-half of patients with squamous NSCLC in Germany (21%), Korea (23%) and Spain (42%). This may be because both histopathological and molecular testing were performed concurrently for some patients. Indeed, at some institutions, such as that of the first author (J.C.), all NSCLC specimens are routinely tested for biomarkers as part of full histopathological characterisation.

The administration of maintenance therapy was relatively infrequent in Korea (7%), the same percentage as reported in a prior study (Sun et al., 2010). This finding could be a reflection of local prescribing practices resulting from reimbursement policy, which stipulated that only patients showing a partial or complete remission could receive maintenance therapy. Alternatively, these findings could reflect a limitation of chart review studies, namely, that continuous maintenance therapy may be difficult to identify from the charts. Relatively low percentages were recorded also in Taiwan (10%), Italy (14%), Australia (16%) and Brazil (17%).

Median overall survival from initiation of first-line therapy ranged from 9.3 months (Brazil) to 25.5 months (Taiwan). Prior studies in Brazil have reported median OS similar to our findings (Araujo et al., 2014; Younes, Pereira, Fares, & Gross, 2011). The median OS of 25.5 months in our Taiwanese cohort could be the result of frequent and appropriate therapy with EGFR TKIs for patients with *EGFR*-positive status, since gefitinib was approved for first-line therapy of *EGFR*-positive NSCLC in Taiwan in June 2011. The median OS of 16.4 and 10.8 months in Italy and Spain, respectively, were similar to earlier findings in European studies (Carrato et al., 2014; Moro-Sibilot et al., 2015).

Our study included real-world patients who presented with newly diagnosed stage IIIB or IV NSCLC and who received first-line systemic therapy, while excluding those enrolled in cancer-related clinical trials. Therefore, patients in this study were likely a different population from those in RCTs. For example, in several countries up to one-fifth of patients had an ECOG performance status of 2 or higher, which would have precluded entry in most trials; likewise brain metastases, an exclusion criterion in some trials, were present in a substantial proportion (20%–25%) of patients in some countries. In Spain, 15% of patients had unknown histology, perhaps because of insufficient biopsy tissue to enable clinical trial participation, which typically requires adequate tissue samples to fully characterise NSCLC.

This study provides a comprehensive, comparative overview of current management strategies for advanced NSCLC in seven countries of the world, with substantial ethnological and practice differences. Our findings reflect racial disparities in European, Asian and mixed populations regarding *EGFR* mutations and *ALK* rearrangements. The study recorded real-world daily clinical practice, providing a snapshot of the complete paradigm of NSCLC treatment from receipt of first-line therapy to death, including up to three lines of therapy. The results depict treatment patterns and predictive biomarker testing practices within the past 3–6 years, providing an update on clinical practices reported in prior observational studies. Most NSCLC is diagnosed at late stages, as for patients in this study. Moreover, we describe the findings by histology as well as by country, illustrating the similarities and variations in clinical practices among the seven countries.

A study limitation is that the staging of NSCLC and the biopsy and biomarker testing procedures were done at individual study centres and were not reviewed by a centralised panel; therefore, there may be variation in practices. We included a mix of academic and community oncology sites, again adding to potential variability in clinical

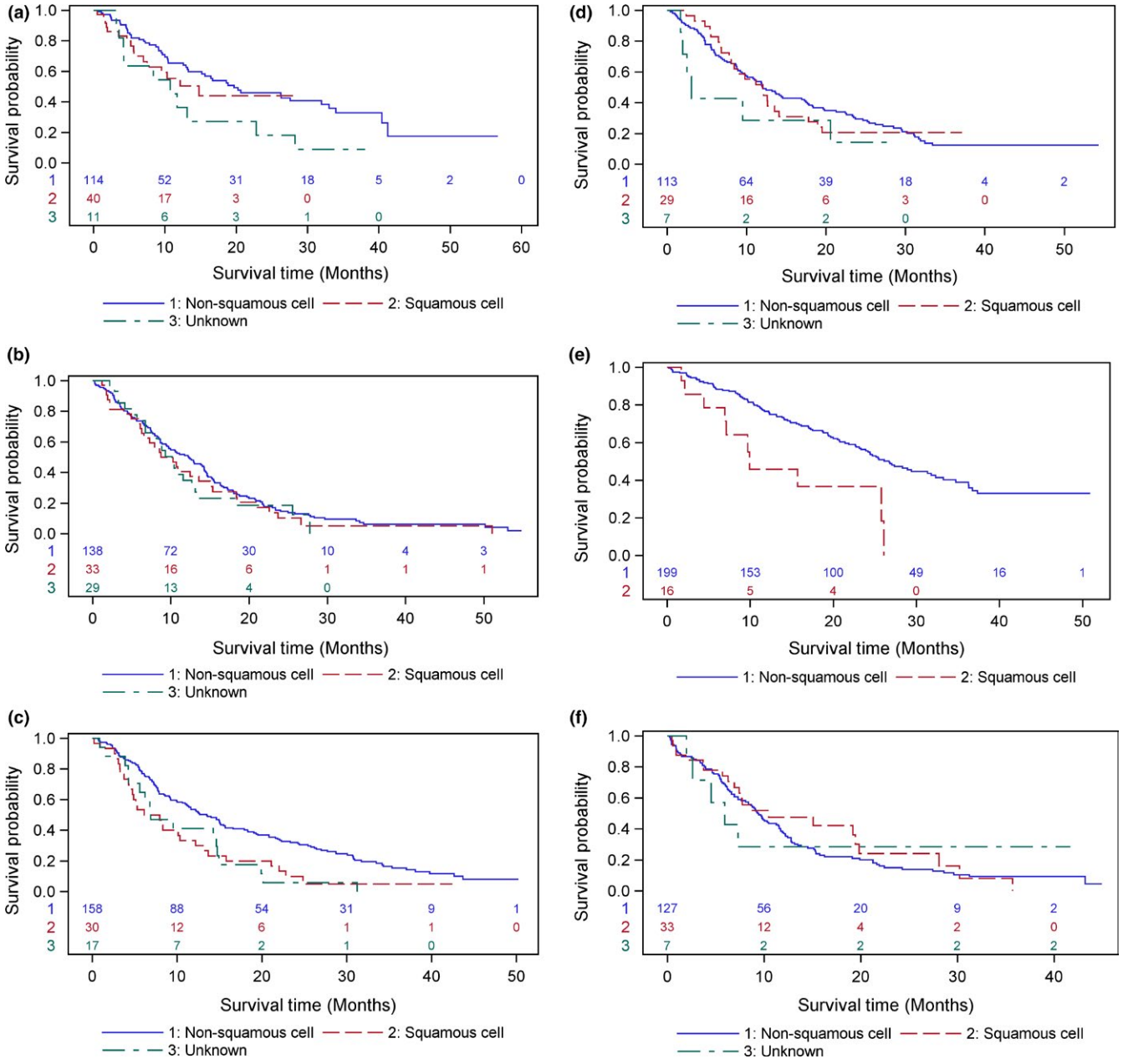

FIGURE 1 Kaplan–Meier plots of overall survival from initiation of first-line therapy by histology for each country: (a) Italy, (b) Spain, (c) Australia, (d) Korea, (e) Taiwan (f) Brazil

practices (van der Linden et al., 2015). Moreover, the data were collected from a convenience sample of study sites that routinely manage patients with NSCLC and therefore may not be representative of country-wide practices. Furthermore, our findings represent treatment approaches and companion diagnostics available at the time the patients were treated and hence may not be reflective of the current landscape of NSCLC management. Finally, while the total study population was large, the sample sizes within each country were relatively modest.

In conclusion, the findings of this study illustrate real-world clinical practice and treatment patterns for advanced NSCLC in seven countries in different regions of the globe. The study provides an aggregate description of treatments and outcomes prior to the introduction of PD-1 and PD-L1 inhibitors for the treatment of NSCLC. Overall, the diagnostic and treatment patterns recorded in this study were heterogeneous but largely in line with NSCLC guideline recommendations during the study years.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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APPENDIX A

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