original reports abstract

Real-World Data on the Prevalence of Anaplastic Lymphoma Kinase–Positive Non–Small-Cell Lung Cancer in the Middle East and North Africa

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PURPOSE Anaplastic lymphoma kinase (*ALK*) gene alterations are potent oncogenic drivers in non–small-cell lung cancer (NSCLC). Tyrosine kinase inhibitors targeting the ALK pathway are effective in treating *ALK*-positive NSCLC. Around 5% of Asian and White patients with NSCLC have *ALK*-positive tumors, but *ALK* rearrangement prevalence data in the Middle East and North Africa (MENA) region are limited.

METHODS In this noninterventional epidemiology study, histologically confirmed nonsquamous NSCLC samples retained for < 5 years in tissue banks at six centers in MENA were retrospectively analyzed for *ALK* rearrangement using the VENTANA immunohistochemistry (IHC) method. Patient characteristics obtained were analyzed for association with *ALK* rearrangement. Concordance between IHC and Vysis fluorescence in situ hybridization (FISH) ALK detection methods was assessed in a subset of samples.

RESULTS Four hundred forty-eight tissue samples were analyzed using IHC: 137 (30.6%) in Lebanon, 104 (23.2%) in Saudi Arabia, 97 (21.7%) in Egypt, 80 (17.9%) in the United Arab Emirates, and 30 (6.7%) in Morocco. On the basis of IHC, the prevalence was 8.7% (95% CI, 6.3 to 11.7) for *ALK*-positivity and 91.3% (95% CI, 88.3 to 93.7) for *ALK*-negativity. On the basis of FISH (n = 148), the prevalence was 5.4% positivity and 81.8% negativity (12.8% nonevaluable). Concordance between IHC and FISH (n = 129) was 98.4% (95% CI, 94.2 to 99.8) for negative agreement and 98.5% (95% CI, 94.5 to 99.8) for overall agreement. Univariate analysis showed that *ALK* rearrangement was significantly associated with epidermal growth factor receptor wild-type status ($P = .03$) but was not significantly associated with sex, race, smoking history, or histologic subtype.

CONCLUSION Our findings suggest that *ALK* rearrangements are more prevalent in MENA than other geographic regions. High concordance was found between FISH and IHC. Except for epidermal growth factor receptor wild-type status, no clinicopathologic characteristics were associated with *ALK*-positive NSCLC.

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INTRODUCTION

Lung cancer accounted for 11.6% (2.1 million) of all new cancer cases and was the leading cause of cancer deaths (18.4% of cancer deaths; 1.8 million people) globally in 2018.[1] Almost 20,000 new cases were recorded that year in Northern Africa and more than 50,000 in Western Asia.[1] Around 85% of lung cancers are non–small-cell lung cancer (NSCLC).[2] Recent advances in the understanding of oncogenic drivers and the development of targeted therapies have resulted in improved survival rates in patients with NSCLC.[2]

Anaplastic lymphoma kinase (*ALK*) gene alterations are potent oncogenic drivers in NSCLC.[3-5] There are now five US Food and Drug Administration–approved ALK-targeted treatments, and second- and third-generation ALK inhibitors also show enhanced activity against CNS metastases.[6] Clinical characteristics associated with *ALK*-positive NSCLC are younger age, adenocarcinoma histology, and lack of smoking history.[3,4] The prevalence of *ALK* rearrangement among patients with NSCLC is around 5%, although rates up to 17% have been suggested.[3,5,7-11] *ALK* rearrangements are predominantly associated with adenocarcinomas,[3,5,7-9,11,12] although it should be noted that other subtypes generally comprise smaller proportions of the populations studied. However, most available epidemiologic data are based on Asian and global White patients, and data regarding the prevalence of *ALK* rearrangement in patients from the overall Middle East and North Africa (MENA) region are limited. One recent study of 566 patients with nonsquamous NSCLC in MENA found few who were tested for *ALK* mutations, with a prevalence of 5.8% (3 of 52 tested patients).[13]

As tyrosine kinase inhibitors targeting the ALK pathway have proven to be effective treatments for patients with

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CONTEXT

Key Objective

To determine the prevalence of anaplastic lymphoma kinase (*ALK*) gene alterations in patients with non–small-cell lung cancer in the Middle East and North Africa population.

Knowledge Generated

Among 448 tissue samples analyzed using immunohistochemistry (IHC), the prevalence was 8.7% (95% CI, 6.3 to 11.7) for *ALK*-positivity and 91.3% (95% CI, 88.3 to 93.7) for *ALK*-negativity. On the basis of the fluorescence in situ hybridization (n = 148), the prevalence was 5.4% positivity and 81.8% negativity (12.8% nonevaluable). Concordance between IHC and fluorescence in situ hybridization (n = 129) was 98.4% (95% CI, 94.2 to 99.8) for negative agreement and 98.5% (95% CI, 94.5 to 99.8) for overall agreement.

Relevance

Larger fraction of patients has *ALK* alteration in the Middle East and North Africa population who would likely benefit for targeted therapy. Using IHC testing is a reasonable frontline testing method to identify this selected group of patients.

ALK-positive NSCLC, screening for *ALK* is important in the diagnostic workup. Development of robust and reliable laboratory tests for predictive biomarkers is also essential to identify patients most likely to benefit from targeted therapy. A variety of methods have been adopted for the detection of *ALK* rearrangement, including fluorescent in situ hybridization (FISH), immunohistochemistry (IHC), and reverse transcriptase polymerase chain reaction (RT-PCR).[14,15] FISH analysis is currently the only US Food and Drug Administration–approved companion diagnostic test to detect *ALK* gene rearrangements, although the test is not readily available in routine diagnostic laboratories. As *ALK* rearrangement frequently involves short intrachromosomal inversion,[14] the resulting subtle changes may also be difficult to interpret by FISH analysis and have led to false-negative results.[16,17]

IHC, an alternative to FISH, can detect *ALK* rearrangements independent of fusion partners; IHC detects the ALK protein itself, which is the target of ALK inhibitors.[14,15] IHC testing for *ALK* rearrangements is routine practice in the MENA region.[18] The VENTANA ALK-IHC assay is the only Conformité Européenne-marked[19] in vitro diagnostics IHC test indicated as an aid in identifying patients eligible for treatment with the ALK inhibitor crizotinib (VENTANA ALK [D5F3] Rabbit monoclonal primary; Roche Diagnostics Middle East Omnipharma S.A.L.).

The primary aim of this retrospective study was to estimate the prevalence of *ALK* rearrangement in NSCLC in the MENA population. The association between *ALK* rearrangement and clinical and pathologic parameters and the concordance between Vysis FISH and VENTANA ALK-IHC methods for *ALK* rearrangement detection were also assessed.

METHODS

Study Design

This was a retrospective, cross-sectional, noninterventional epidemiologic study to investigate the prevalence of *ALK* rearrangement in patients with NSCLC in MENA. The study was conducted in six centers in five countries: Lebanon (American University of Beirut Medical Center), the United Arab Emirates (UAE; Tawam Hospital, Al Ain), the Kingdom of Saudi Arabia (KSA; two centers: King Faisal Specialist Hospital and Research Center, Riyadh, and King Abdulaziz Medical City, National Guard Hospital, Riyadh), Egypt (National Cancer Institute, Cairo), and Morocco (Institut National d'Oncologie, Rabat).

Retrospectively collected, nonsquamous NSCLC tumor specimens were identified and retrieved from the tissue banks of the study center molecular diagnostic units and pathology departments. All samples were analyzed for *ALK* rearrangement at each center using the VENTANA ALK-IHC method and at each of the study centers. A subset of samples (at three centers) was also tested using the Vysis FISH method, and the concordance of the FISH and IHC results was analyzed. Patient characteristics such as demographic, clinical, and pathologic parameters were obtained from medical records and were analyzed for association with the presence of the *EML4-ALK* fusion gene.

Patients and Samples

Samples included were from adult patients (age $>$ 18 years) diagnosed or treated at one of the study centers in the past 5 years with histologically confirmed nonsquamous NSCLC and with tissue that is of sufficient quantity and quality (age $<$ 5 years) for *ALK* testing. Only routinely processed formalin-fixed, paraffin-embedded tissue samples were eligible for analysis, and histological sections mounted on glass slides must not have been older than 3 months.

This study was conducted in accordance with established research principles and Good Clinical Practice guidelines. As this was a retrospective epidemiology study, no patients were enrolled. Patients had already provided written informed consent (for general investigational testing or for

specific testing for this study) or had a documented waiver for informed consent document use, as required by local regulatory authorities and/or the site Research Ethics Committee and/or Institutional Review Board.

Analytical Methods

All eligible NSCLC samples were tested using the VENTANA ALK-IHC method, and a subset was tested using Vysis FISH.

IHC testing was performed using the VENTANA anti-ALK (D5F3) primary antibody, developed for use on VENTANA BenchMark XT and BenchMark GX–automated slide stainers, in combination with Rabbit Monoclonal Negative Control Ig, OptiView DAB IHC Detection Kit, and OptiView Amplification Kit and accessories. Sections approximately 4 μm thick were mounted onto positively charged glass slides and stained within 3 months after cutting. *ALK* status was determined in accordance with the VENTANA kit manufacturer's guidance (VENTANA anti-ALK [D5F3] Scoring Interpretation Guide and Performance Characteristics). *ALK*-positivity was defined as the presence of strong granular cytoplasmic staining in tumor cells (any percentage of positive tumor cells).

FISH analysis was performed on a subset of the FFPE tumor tissue samples using a break apart probe specific to the *ALK* locus (Vysis LSI ALK Dual Color, break apart rearrangement probe [Vysis ALK Break Apart FISH Probe Kit]), Abbott Molecular according to the manufacturer's instructions. Briefly, 4-μm-thick sections were deparaffinized, dehydrated, immersed with Vysis pretreatment Solution (Abbott Molecular, Des Plaines, IL) at 80°C for 15 minutes, and treated with Protease Solution (Abbott Molecular) at 37°C for 20 minutes. Dual probe hybridization was performed using the locus specific identifiable *ALK* dual-color probe, which hybridizes to the 2p23 locus with Spectrum Orange and Spectrum Green on either side of the *ALK* gene break point. The FISH result was considered positive when more than 15% of 50 or more analyzed cells showed splitting of the fluorescent probes flanking the *ALK* locus.

Statistical Analyses

An initial quasirandom pilot sample was taken of records from the combined discharge populations' records at the selected sites; no minimum sample was determined before this manual review, but as many charts as possible were reviewed to maximize precision for the incidence estimates. Tissue samples from approximately 700 patients were planned to be included in the study. Assuming an expected prevalence of ≤ 10%, a sample size of 700 patients permitted estimation of the percentage of patients with *EML4-ALK* fusion to within ±2.1% with a 95% CI (ie, the half-width of the 95% CI will be < 2.2%).

Clinical and histopathologic characteristics of *ALK*-positive tissue samples were compared with those of the *ALK*-negative tissue samples. Analyses were based on the full analysis set, defined as all included cases with tissue samples that met the selection criteria. Analyses were primarily descriptive in nature. Binary data were summarized using the percentage of patients with the event and a 95% CI. Continuous data were reported using n, mean, standard deviation, median, and range; a 95% CI for the mean was also computed. Descriptive statistics were given for the entire population. Missing data were marked as unknown.

The primary end point, prevalence of *ALK* rearrangement, was calculated as 100 × the number of cases with *ALK* rearrangement divided by the total number of cases in the full analysis set. Secondary end points were analyzed as follows: univariate comparison between the proportion of patients with *ALK* rearrangement within categories of demographic, clinical, and pathologic parameters was summarized using *P* values of chi-square tests, odds ratios, and 95% CIs for the odds ratios. A logistic regression analysis was performed using the presence of *ALK* rearrangement as the dependent variable. Independent variables included in the model were as follows: sex, race, smoking history, tumor histologic diagnosis and stage, treatment type, progression-free survival at 6 months after treatment, line of therapy, overall response, patient status, and epidermal growth factor receptor (*EGFR*) and Kirsten rat sarcoma viral oncogene homolog (*KRAS*) status. A stepwise method was used for the selection of independent variables. The concordance between Vysis *ALK*-FISH and VENTANA ALK-IHC tests (only on tissue samples with evaluable assessments for both tests) was evaluated by the assessment of positive, negative, and overall percentage agreement between tests and associated 95% CIs.

All statistical tests were performed two-sided and at a type 1 error (*P* value) probability of $\alpha = .05$. All CIs were derived two-sided and at a confidence probability of $1-\alpha = .95$. Statistical analyses were performed using SAS for Windows (version 9.3).

RESULTS

Patients and Samples

Demographic characteristics of the 448 patients are presented in Table 1. Most patients were male (68.8% overall) and Arabic or White (98.7% overall), with a mean age at NSCLC diagnosis of 60.5 years. Almost half (48.9%) of the patients were current or ex-smokers, although smoking status was unknown for just over a quarter (26.3%).

The most frequent histologic diagnosis was adenocarcinoma (n = 430, 96.0%), followed by large cell carcinoma (n = 6, 1.3%). The most common tumor stage was stage IV (n = 260, 58.0%), followed by stage III (n = 62, 13.8%), stage II (n = 51, 11.4%), and stage I (n = 32, 7.1%). Data were missing for 43 patients (9.6%).

Patients received the following prior treatments: chemotherapy only (n = 154, 34.4%), surgery without chemotherapy

TABLE 1. Patient Characteristics

Characteristic	Lebanon (n = 137)	KSA (n = 104)	Egypt (n = 97)	UAE (n = 80)	Morocco (n = 30)	Overall (N = 448)
Age at diagnosis, mean (SD), years	63.2 (11.2)	61.8 (13.0)	56.7 (10.9)	58.8 (13.1)	57.8 (7.8)	60.5 (12.0)
Sex: Male, No. (%)	76 (55.5)	76 (73.1)	77 (79.4)	57 (71.3)	22 (73.3)	308 (68.8)
Race, No. (%)						
Arabic or White	137 (100.0)	102 (98.0)	97 (100.0)	76 (95.0)	30 (100.0)	442 (98.7)
Others	—	2 (1.9)	—	3 (3.8)	—	5 (1.1)
Missing	—	—	—	1 (1.3)	—	1 (0.2)
Smoking history, No. (%)						
Never	36 (26.3)	16 (15.4)	19 (19.6)	33 (41.3)	7 (23.3)	111 (24.8)
Current	58 (42.3)	26 (25.0)	23 (23.7)	12 (15.0)	14 (46.7)	133 (29.7)
Ex-smoker	30 (21.9)	15 (14.4)	13 (13.4)	21 (26.7)	7 (23.3)	86 (19.2)
Unknown	13 (9.5)	47 (45.2)	42 (43.3)	14 (17.5)	2 (6.7)	118 (26.3)
Age at death, mean (SD), years	67.1 (10.9) (n = 22)	63.9 (10.7) (n = 25)	62.1 (11.6) (n = 7)	61.7 (11.2) (n = 31)	— (n = 0)	63.8 (11.0) (n = 85)

Abbreviations: KSA, Kingdom of Saudi Arabia; SD, standard deviation; UAE, United Arab Emirates.

(n = 58, 13.0%), surgery with chemotherapy (n = 53, 11.8%), and targeted therapy (n = 10, 2.2%). Treatment status was other or unknown for 173 patients (38.6%). Of the 154 patients who received chemotherapy only, 18 (11.7%) received pemetrexed either alone or as part of a combination therapy. Most patients received a first-line therapy only (n = 219, 48.9%); 59 (13.2%) received two lines of therapy or more. Data were missing or unknown for 170 patients (37.9%).

Overall response data were as follows: 28 patients (6.3%) had a complete response, 15 (3.4%) had a partial response, 56 (12.5%) achieved stable disease, and 157 (35.0%) experienced progressive disease. The overall response was unknown for 191 patients (42.6%). The median time from the start of the treatment to relapse was 227.0 days (n = 145).

The mean (±standard deviation) duration between diagnosis and tissue sampling was 142.1 (±444.9) days (median 1.0 day). At the time of tissue sampling, most patients (n = 415, 92.6%) were treatment naive, 27 (6.0%) were treated, and treatment status was unknown for six (1.3%) patients. Three quarters (n = 337, 75.2%) of tissue samples were removed during a biopsy, 94 (21.0%) were surgically resected, and five others (1.1%) were reported (abdominal subcutaneous parietal tumor, left breast nodule, lymph node, fine-needle aspiration, and pleura) while the specimen type was unknown for 12 (2.7%) specimens.

EGFR mutation status was wild type for 148 patients (33.0%) and mutant type for 61 patients (13.6%). *EGFR* status was not tested for 208 (46.4%) samples and was unknown for three (0.7%) samples (28 samples [6.3%] had other status reported: insufficient, negative, failed, and unable to evaluate). Most samples (n = 433, 96.7%) were not tested for *KRAS* status. Of the 15 samples tested, six expressed wild-type *KRAS* and seven expressed mutant *KRAS*.

Prevalence of *ALK* Rearrangement

All 448 samples were analyzed by IHC for the *ALK* rearrangement, 148 were analyzed by FISH (Fig 1A). Evaluable data from both tests were available for 129 samples (Fig 1B). On the basis of IHC testing, the overall prevalence was 8.7% (95% CI, 6.3 to 11.7) for *ALK*-positivity and 91.3% (95% CI, 88.3 to 93.7) for *ALK*-negativity. None of the 61 patients with *EGFR* mutations were *ALK*-positive by using IHC. *ALK*-positivity prevalence was highest in Egypt (19.6%) and lowest in Lebanon (2.2%). The overall result from FISH testing was 5.4% for *ALK*-positivity and 81.8% (12.8% of samples were nonevaluable) for *ALK*-negativity.

Association Between *ALK* Rearrangement and Demographic, Clinical, and Pathologic Parameters

On the basis of the univariate comparison between the overall proportion of patients with *ALK* rearrangement and demographic, clinical, and pathologic parameters, *ALK*-IHC rearrangement was significantly associated with *EGFR* mutation status (wild type; $P = .03$). *ALK* rearrangement was not significantly associated with any of the following parameters (all $P > .05$): sex, race, smoking history, tumor histological diagnosis, tumor stage, treatment type, line of therapy, overall response, or patient status (treatment naive versus treated). As *KRAS* status was known only for 13 samples, it was not possible to reliably assess whether *ALK* rearrangement was associated with *KRAS* status.

In the stepwise (backward) logistic regression analysis, *ALK* rearrangement (on the basis of *ALK*-IHC or *ALK*-FISH) was not significantly associated with any of the parameters assessed.

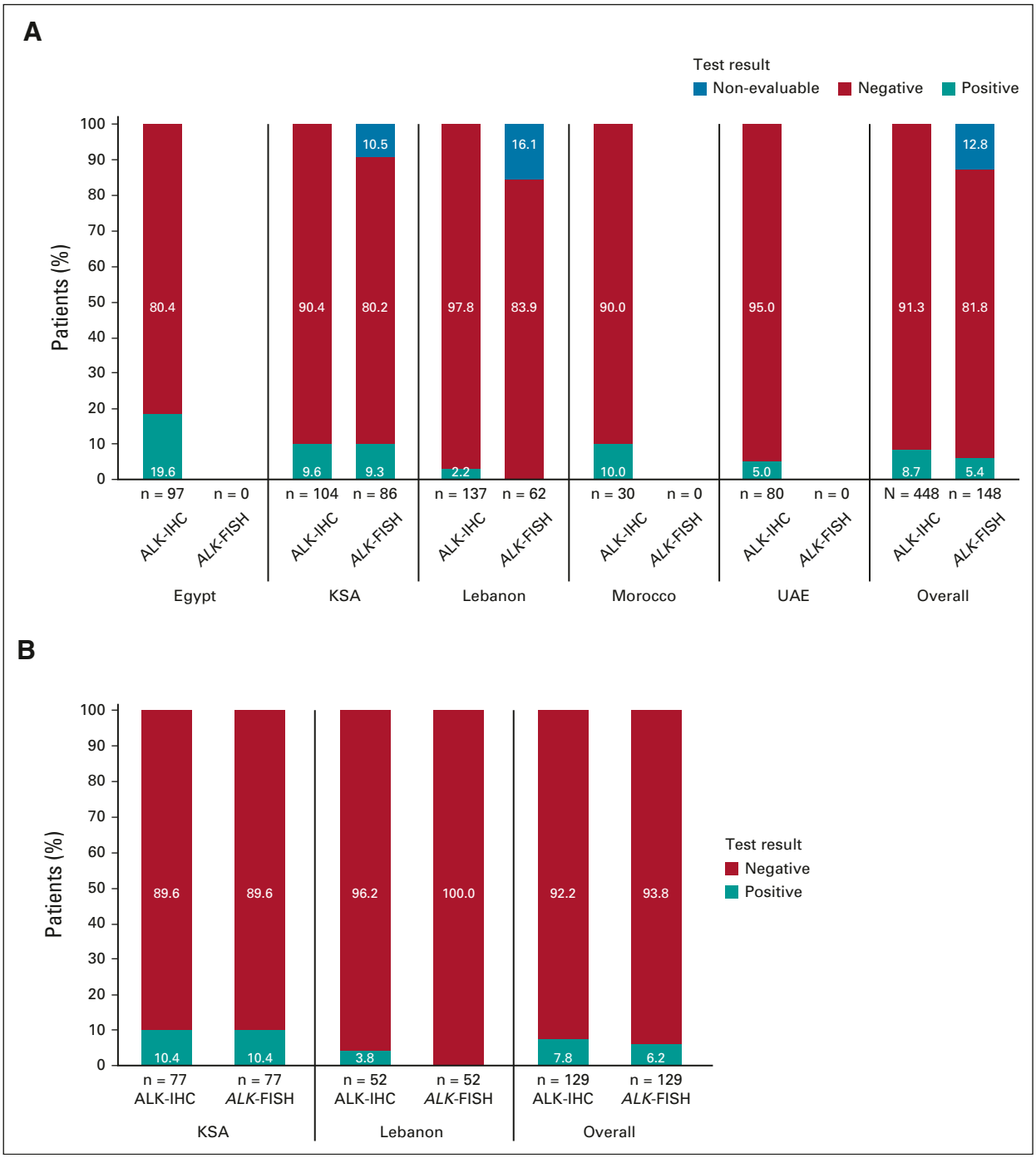

FIG 1. Prevalence of *ALK* rearrangement on the basis of ALK-IHC and *ALK*-FISH analyses: (A) all results and (B) patients with evaluable data from both tests only. ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates.

Concordance Between Vysis *ALK*-FISH and VENTANA ALK-IHC Tests

Concordance between IHC and FISH was analyzed in the subset of samples (from 77 patients in the KSA and 52 patients in Lebanon) with evaluable data from both tests (Fig 1B). Negative agreement for *ALK* rearrangement detection among these patients from KSA and Lebanon was 98.4% overall (95% CI, 94.2 to 99.8), 100.0% in KSA (95% CI, 94.8 to 100.0), and 96.2% in Lebanon (95% CI, 86.8 to 99.5).

Overall agreement between both methods for KSA and Lebanon combined was 98.5% (95% CI, 94.5 to 99.8).

Positive agreement between both methods was 100% in KSA (95% CI, 63.1 to 100).

DISCUSSION

This retrospective analysis of tissue samples from patients with NSCLC suggested that *ALK*-positivity may be higher in the MENA region than other geographic regions, although our samples included only patients with nonsquamous histology. Overall *ALK*-positivity prevalence was 8.7% by using IHC; *ALK*-positivity was highest in Egypt (19.6%) and lowest in Lebanon (2.2%). In our univariate analysis, only *EGFR* wild-type status was significantly associated with *ALK*-IHC rearrangement; other parameters, including race, showed no significant association.

Our overall prevalence data are generally in line with those previously observed for the MENA[1,13] region and a recent retrospective analysis in Morocco.[20] Another study reported *ALK*-positivity of 11.8% on the basis of the results from the full population of 152 patients with nonsquamous NSCLC in Lebanon tested by using IHC and 3.9% overall on the basis of testing of the patients tested IHC-positive by using FISH.[21] Studies on patients with lung adenocarcinoma in Tunisia and the Levant region found *ALK*-positivity of 1.4% and 1.9% on the basis of the results from 73 patients tested by using IHC[22] and 157 patients tested by using FISH, respectively.[23] Published data regarding the prevalence of *ALK* rearrangement among patients with NSCLC globally are generally around 5%, although both lower and higher rates have been reported in different regions and populations on the basis of race and smoking status, and the proportions of different NSCLC subtypes vary between studies.[3,5,7,11,18] Evidence of variations according to race includes some reports of lower *ALK* rearrangement prevalence in Asian patients. Data of Chinese patients from another study were within this range, with a 4.1% prevalence of *ALK* fusions; frequencies were 5.1% in tissue samples and 3.3% in plasma samples,[24] suggesting that some variations in reported prevalence may be due to sample and test type. A meta-analysis also reported lower prevalence in Asian versus non-Asian patients, although rates were slightly higher than those observed by Shaw et al,[7] with 6.1% observed in Asian patients versus 8.5% in non-Asian patients.[25] However, as *ALK*-positivity is more frequent in light smokers and never-smokers, it has been suggested that this may result in a higher prevalence in Asian countries.[9] A high prevalence of 14.8% in Asian patients was reported by Yamaguchi et al[11] compared with 7.8% in White patients and 0% in Black patients. Our study found no significant association between *ALK*-positivity and race, although this may be due to the population being mostly Arabic or White.

An association between *ALK*-positivity and male sex has been reported previously,[7,8] although Zhao et al[25] found a slightly (but not significantly) higher rate in women. The concordance between IHC and FISH results was high in our study. This is in line with other studies reporting high condordance.[15] Since the availability of tissue and checking for multiple actionable targets in lung cancer are major challenges, next-generation sequencing is the preferred method for testing when accessible.[15]

Although our study provides new information on previously lacking data for *ALK*-positivity in patients with NSCLC in the MENA region, it is subject to the limitations typically associated with a retrospective, cross-sectional study. These include bias associated with retrospective data collection and considerations regarding missing and incomplete data (set to missing for any calculation in the analysis). For example, data were missing for several demographic parameters such as smoking history; these data were not available for all patients as some were not treated or followed up in the centers. As most samples (75.2%) were from lung biopsies, the limited cell numbers in some lung biopsies resulted in their exclusion from the study because of insufficient testing material. Our sample size of 448 was also below our planned size of 700. This may have limited the power to detect statistically significant associations between patient characteristics and *ALK*-positivity but was considered sufficient to assess the correlation between data obtained using IHC and FISH. Our prevalence percentages are based only on patients tested for evidence of *ALK* rearrangement by using IHC and/or FISH, but the reporting of data on the basis of varying denominators (eg, full population versus tested population) in other studies also complicates comparisons between studies. Although we included only patients with nonsquamous histology, squamous histology accounts for a smaller proportion of NSCLC cases (approximately 30%)[26] and *ALK* rearrangements are mainly associated with adenocarcinomas.[3,5,7,9,11,12] As we included a nonsquamous population more associated with *ALK* rearrangement, this may have contributed to our higher percentage of *ALK*-positivity than seen in some other studies. Although the proportions of different NSCLC subtypes vary between studies,[3,5,7,11,18] squamous histologies typically make up a relatively small proportion as may be expected in line with their lower prevalence compared with nonsquamous disease. The variability in *ALK*-positivity rates may also be affected by the method of analysis used and the sample size. In a study of Moroccan patients with advanced NSCLC (all histologies), two of 90 patients (2.2%) tested positive by using FISH and three of 30 patients (10%) tested positive by using IHC, with the overall frequency stated as 5 of 120 (4.2%).[20] Differences between studies in terms of population, sample size, and analytical techniques also limit the ability to reliably compare data from different regions.

Although we found no statistically significant associations between patient characteristics (other than *EGFR* wild-type status) and *ALK*-positivity, the low prevalence of *ALK*-positivity in Lebanon may have been influenced by patient characteristics. Characteristics previously associated with *ALK*-positivity include younger patients, male sex, and a

never or light smoking history.[7,8,15,27] In our study, patients in Lebanon had a higher mean age and lower proportion of males, compared with those from the other countries, and most patients from all countries studied with known smoking status were current or ex-smokers. In contrast, patients in Egypt, where the *ALK*-positivity was higher than reported, had a lower mean age and higher proportion of males.

Although our study found high concordance between data obtained by using IHC and FISH, we acknowledge that this was based on only two (KSA and Lebanon) of the five countries from our overall analysis (as only KSA and Lebanon performed FISH) and that Lebanon had the lowest overall *ALK*-positivity of all the countries we studied (2.2% by using IHC, no cases by using FISH). Our results may suggest a higher rate of false-positive results using IHC, although other studies have also reported instances of discordance between IHC and FISH; some discordant cases have been suggested to be due to differing biological features of the disease which may have an impact on treatment strategy.[28,29]

This retrospective analysis of a real-world sample allowed an assessment of overall prevalence in MENA but may have limited the ability to assess associations between demographic and clinical characteristics and *ALK*-positivity. For example, the median age of patients in this study was 61 years. Patients with *ALK* rearrangement tend to be younger than most patients with NSCLC, with the reported median age of 52-55 years.[8,15] This may have resulted in an underestimate of prevalence in a population that included a higher proportion of younger patients and limited the ability to assess the association with age. The focus on the MENA regions resulted in most samples being from Arabic or White patients; the lower numbers of patients from other ethnic groups may explain why no association between race and *ALK*-positivity was observed.

In conclusion, our findings suggest that the prevalence of *ALK* rearrangement may be higher in the MENA region than typically reported for many other countries or ethnic groups. A high level of concordance was found between FISH and IHC for *ALK* rearrangement detection. Except for *EGFR* wild-type status, no clinicopathological characteristics for patients with *ALK*-positive NSCLC were identified. Testing for *ALK* and *EGFR* mutations is routine in most MENA countries,[18] and the relatively high prevalence of *ALK*-positivity in some countries in our study supports the importance of testing to ensure that the most appropriate targeted therapy is given.

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DATA SHARING STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual anonymized participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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