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Epidemiological Characteristics, *EGFR* Status and Management Patterns of Advanced Non-small Cell Lung Cancer Patients: The Greek REASON Observational Registry Study

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Abstract. *Background/Aim: Real-world evidence regarding the prevalence of epidermal growth factor receptor (EGFR) mutation-positive status (M+) and the clinicopathological characteristics associated with the presence of EGFR mutations in advanced non-small cell lung cancer (NSCLC) is scarce, especially among Caucasian populations. The present study aimed to bridge this gap, as well as to record treatment patterns and outcomes in routine-care settings. Patients and Methods: REASON (NCT01153399) was a prospective study of patients with stage IIIB/IV NSCLC and known EGFR mutation status. Clinicopathological, treatment characteristics and clinical outcomes were recorded and correlated with EGFR mutation testing results. Results: Of 575 enrolled patients, EGFR mutations were detected in 15.7% of them. Male gender (p=0.008) and smoking (p<0.001), but not adenocarcinoma, were associated with EGFR M+ status. In the EGFR M+ subpopulation (n=88), absence of bone and/or brain metastasis and presence of exon 19 EGFR M+ status at diagnosis were independently associated with longer progression-free survival (PFS) (p=0.011 and p=0.040, respectively). Conclusion: In our population, males and smokers had decreased odds of harboring an EGFR mutation, while adenocarcinoma histology was not a significant predictor of EGFR M+ status. EGFR M+ patients with bone and/or brain metastases at diagnosis or mutations other than exon 19 deletions were at increased risk for earlier disease progression.*

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In 2012, 353,000 deaths in Europe were attributed to lung cancer, the most common cause of cancer-related deaths. In Greece, lung cancer was estimated to be the leading cause of cancer-related deaths among men (age standardized rate (ASR): 67.7 per 100,000), and the second leading cause of cancer-related deaths among women (ASR: 11.8 per 100,000), while its incidence was ranked highest in men (ASR: 74.7 per 100,000), and as the third highestin women (ASR: 13.2 per 100,000) after breast and colorectal cancer (1).

Non-small cell lung cancer (NSCLC) comprises about 85% of all lung cancer diagnoses (2). Most NSCLC patients are initially diagnosed at an unresectable locally advanced (stage IIIB) or metastatic (stage IV) stage (3). Prognosis of stage IIIB/IV NSCLC is poor, with a median overall survival (OS) of about 10 months (4), and a 5-year relative survival rate of metastatic disease of merely 4.5% based on 2007-2013 data from the Surveillance, Epidemiology, and End Results Program (5).

Routine treatment strategies for stage IIIB/IV NSCLC include chemotherapy, radiotherapy and targeted therapy and are guided by tumor histological subtype, molecular profiling and genetics, as well as the patient's age, performance status (PS) and preferences (6-8). The addition of targeted agents to the treatment armamentarium of NSCLC was a major breakthrough, offering clinically meaningful benefits for patients harboring epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase 1 (*ALK1*) mutations, as well

as ROS1 rearrangements. EGFR tyrosine kinase inhibitors (EGFR-TKIs) and ALK1-TKIs have provided a paradigm shift in the management of advanced NSCLC, representing the pioneers of personalized treatment options and solidifying the importance of molecular testing as part of the diagnostic algorithm (9, 10).

The frequency of *EGFR* mutation-positive (M+) tumors is much higher among Asian-Pacific (30-50%) (3,11-14) than Caucasian (10-17%) populations (15-20). Additionally, a positive *EGFR* mutation status has been associated with a non-smoking history, female sex and adenocarcinoma histology (3, 10). High NSCLC incidence and mortality in Greece along with the anticipated interethnic variations in terms of genetic profile and treatment outcomes of those patients fueled the need for conduct of real-life epidemiological studiesat a country level. Thus,essential information could be recorded in order to support evidence-informed decision-making for the routine-care management of advanced NSCLC disease.

Under this perspective, the present study sought to collect epidemiological data regarding *EGFR* mutation status from patients with stages IIIB/IV NSCLC in Greece and determine its association with smoking status, gender, and tumor histology. In addition, the study aimed to capture information on clinical outcome data (progression-free survival (PFS), OS and disease control rate (DCR), first-line treatment patterns employed in stage IIIB/IV NSCLC patients, regardless of *EGFR* mutation status and gain preliminary insight on the healthcare resource utilization of *EGFR* M+ patients treated in routine care settings.

Materials and Methods

Study design, population and setting. REASON (NCT01153399) was a multicenter, prospective observational study, carried out by 22 hospital-based physicians specializing in oncology (n=19) or lung diseases (n=3) from representative geographic regions of Greece. Consecutive enrollment of patients attending the study sites that met the study specific eligibility criteria was employed as means to control for and minimize patient selection bias. Routine assessments were performed under real-life conditions without intervening in patient selection, diagnostic procedures employed, or therapeutic decision-making.

At enrollment, for all patients with histologically confirmed stage IIIB/IV NSCLC and *EGFR* mutation-negative (M–) or *EGFR* non-evaluable (Mx) status, as well as those with *EGFR* mutation-postive (M+) status who wished to participate in any interventional trial, data pertaining to clinicopathological characteristics and first line treatments were collected; for these patients, participation was completed at the enrollment visit. For *EGFR* M+ patients for whom participation in an interventional study was not foreseen, study participation ended one year after the last patient was included into the study, unless the patient i) wished to end his/her participation in the study earlier, ii) experienced disease progression or died, or iii) was lost to follow-up. Study follow-up information for these *EGFR* M+ patients included response evaluation based on the treating physician's routine assessments and without mandating the use of standardized tumor response evaluation criteria, survival status and healthcare resource utilization. All study data were recorded on paper case report forms.

The study was performed in accordance with the International Society for Pharmacoepidemiology guidelines for Good Pharmacoepidemiology Practice, the ICH-GCP guidelines (where applicable) the ethical principles of the Declaration of Helsinki and all standing regulations. As per the national regulations, the original study protocol including the final version of the patient's Informed Consent Form (ICF), were reviewed and approved by the competent institutional review boards of the participating Hospital Sites and by the Greek National Organization for Medicines (EOF), before the enrollment of any patient into the study and the performance of any study-related procedure. There was one protocol amendment (extending the recruitment period and increasing the number of participating sites in order to meet the study target) which was approved by the IRBs of the participating hospitals as per the standing national regulations.

Study population. The eligible study population comprised of newly diagnosed and untreated males and females aged ≥18 years with histologically confirmed stage IIIB/IV NSCLC and known *EGFR* mutation status (*i.e*. *EGFR* M+, *EGFR* M– or Mx), who at enrollment were treated in the first-line setting and whose tumor was not amenable to curative surgery or radio-chemotherapy. Patients with mixed histology of small and non-small cell lung cancer were excluded from the study.

Study objectives and endpoints. The study primarily aimed to collect epidemiological data on the frequency of *EGFR* M+ NSCLC in a population of predominantly Caucasian ethnicity, and to elucidate the association of smoking status, gender and tumor histology with *EGFR* mutation status. Secondary study objectives were to capture the real-life management patterns in the overall population and *EGFR* M+, M– and Mx subpopulations, and to assess clinical outcomes (PFS, OS, DCR) and healthcare resource utilization in terms of hospitalizations and outpatient visits in routine care settings of Greece among *EGFR* M+ patients.

Statistical methods. All enrolled patients with histologically confirmed stage IIIB/IV NSCLC and with available *EGFR* mutation status information have been included in the analysis of the primary aim of the study (Full Analysis Set – FAS). Patients fulfilling all eligibility criteria have been included into the dataset for the evaluation of secondary endpoints (Per Protocol Analysis Set – PP).

The association of smoking status, gender and histological type with the *EGFR* mutation status was examined through simple logistic regression analysis as well as by a multiple logistic regression model. In order to estimate the median PFS and OS times, the Kaplan–Meier method was applied. Association of age at the time of diagnosis (>65 years *vs*. ≤65 years), smoking status at enrollment (never smoker *versus* smokers), histological subtype at initial diagnosis (non-adenocarcinoma *versus* adenocarcinoma), presence of bone and/or brain metastases, presence of exon 19 mutation with PFS was assessed through a multivariable Cox proportional hazard model estimating the hazard ratios (HR) and the relevant 95% confidence intervals (CIs). DCR has been defined as the percentage of patients who had achieved at least a complete response, partial response or stable disease. Clopper-Pearson 95%

City, Region of Greece	Sites	Participants enrolled
1. Kavala, Eastern Macedonia and Thrace	1	5
2. Thessaloniki, Central Macedonia	4	113
3. Ptolemaida, West Macedonia	1	4
4. Ioannina, Epirus	1	9
5. Larissa, Thessaly	1	9
6. Athens, Attica	12	315
7. Patras, West Greece	1	37
8. Heraklion, Crete	1	97
Total	**22**	**589**

Figure 1. *Geographic distribution of study sites and enrolled population.*

exact CIswere calculated. The hospitalization and outpatient visit rates expressed in person-years have been calculated by dividing the total number of hospitalizations and outpatient visits respectively, by the 'patient-year at risk' time, *i.e.* the days elapsed from enrollment to study completion period divided by 365.25 to obtain the actual period in years. No imputation of missing data has been performed with the exception of partial dates. All statistical tests were two-sided and were performed at a 0.05 significance level. Statistical analysis has been conducted using SAS® v9.3 (SAS Institute, Cary, NC, USA).

Sample size. Under the assumption that, in the present study, the proportion of *EGFR* mutation positive (M+) NSCLC subjects would be 12%, the assessment of 450 subjects was required in order to detect this rate at the significance level of 0.05, with 80% power and an approximate±0.03 points (95%CI=9-15%) precision, using a two-tailed test (Relative Standard Error: 12.77%). Therefore, accounting for a 25% non-evaluable rate, approximately 600 patients were finally proposed to be included in the study.

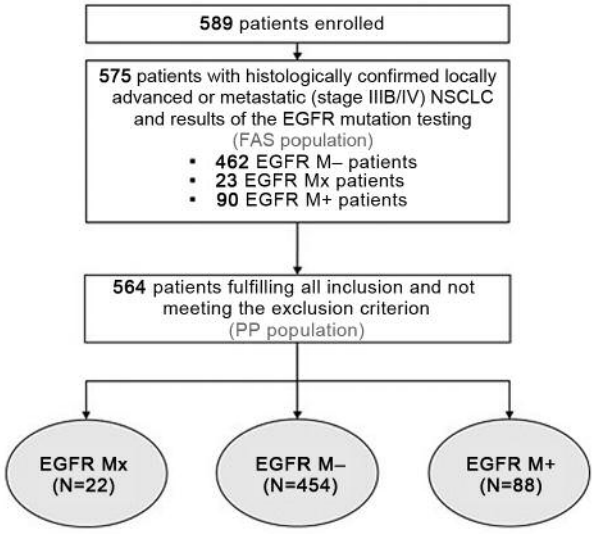


Figure 2. *Patient disposition per EGFR mutation status and study analysis sets. FAS: Full analysis set; PP population: per protocol population (eligible patients).*

Results

Patient characteristics. Between 13 October 2010 and 19 December 2013 a total of 589 Caucasian patients were enrolled in the study by 22 study sites located throughout Greece (Figure 1). The overall study duration was approximately 4 years, with the last patient last visit occurring on 18 December 2014. Patient disposition in the FAS population (N=575) and the PP population (N=564) is illustrated in Figure 2.

The median age of the overall population (FAS) at enrollment was 65.6 years (range=35.9-87.0 years); 73.4% (422/575) were males, and 82.6% (475/575) were either current or former smokers (Table I). Patients with adenocarcinoma comprised 81.4% (468/575) of the overall population and those with ECOG PS 0 or 1, 88.3% (508/575). Among patients with known data, the primary tumor was mainly localized in the right upper lobe (41.8%; 233/557), left upper lobe (27.5%; 153/557) and the right inferior lobe (24.2%; 135/557). At initial diagnosis, the vast majority of the overall population (93.6%; 538/575) presented with late stage (IIIB/IV) disease at initial diagnosis (37 patients presented with early stage disease at initial diagnosis). The most common sites of metastases were the bones (31.1%; 179/575) and the brain (17.7%; 102/575). Sociodemographic, anthropometric and clinical characteristics of the subpopulations per *EGFR* mutation status are reported in Table I.

Table I. *Sociodemographic, anthropometric and clinical characteristics of the overall population and subpopulations per EGFR mutation status.*

Patient characteristics	Overall population (N=575)	*EGFR* M+ (N=90)	*EGFR* M– (N=462)	*EGFR* Mx (N=23)
Gender (n, %)				
Female	153 (26.6%)	51 (56.7%)	96 (20.8%)	6 (26.1%)
Male	422 (73.4%)	39 (43.3%)	366 (79.2%)	17 (73.9%)
Smoking status at enrollment (n, %)				
Never smoker (lifetime exposure to <100 cigarettes)	100 (17.4%)	49 (54.4%)	51 (11.0%)	-
Former smoker (has quit smoking for >12 months)	180 (31.3%)	22 (24.4%)	148 (32.0%)	10 (43.5%)
Current smoker (including those who have quit within the past 12 months)	295 (51.3%)	19 (21.1%)	263 (56.9%)	13 (56.5%)
Past conditions/Comorbidities at enrollment* (n, %)				
Hypertension	166 (28.9 %)	33 (36.7 %)	122 (26.4 %)	11 (47.8 %)
Diabetes mellitus	81 (14.1 %)	10 (11.1 %)	67 (14.5 %)	4 (17.4 %)
Dyslipidemia	64 (11.1 %)	12 (13.3 %)	45 (9.7 %)	7 (30.4 %)
Coronary artery disease	70 (12.2 %)	7 (7.8 %)	61 (13.2 %)	2 (8.7 %)
ECOG performance status at enrollment (n, %)				
0	228 (39.7%)	35 (38.9%)	186 (40.3%)	7 (30.4%)
1	280 (48.7%)	50 (55.6%)	218 (47.2%)	12 (52.2%)
2	56 (9.7%)	4 (4.4%)	49 (10.6%)	3 (13.0%)
3	11 (1.9%)	1 (1.1%)	9 (1.9%)	1 (4.3%)
Tumor histological type at first diagnosis (n, %)				
Adenocarcinoma	468 (81.4%)	77 (85.6%)	371 (80.3%)	20 (87.0%)
Squamous cell carcinoma only	60 (10.4%)	7 (7.8%)	52 (11.2%)	1 (4.3%)
Large cell carcinoma only	14 (2.4%)	1 (1.1%)	13 (2.8%)	-
Others	33 (5.7%)	5 (5.6%)	26 (5.6%)	2 (8.7%)
Tumor localization at first diagnosis (n, %)				
Right lung only	325 (56.5%)	41 (45.6%)	270 (58.4%)	14 (60.9%)
Left lung only	189 (32.9%)	36 (40.0%)	147 (31.8%)	6 (26.1%)
Right and left lung	43 (7.5%)	8 (8.9%)	32 (6.9%)	3 (13.0%)
Unknown	18 (3.1%)	5 (5.6%)	13 (2.8%)	-
Disease stage at first diagnosis (n, %)				
Stage I/II	16 (2.8%)	3 (3.3%)	13 (2.8%)	-
Stage IIIA	18 (3.1%)	2 (2.2%)	14 (3.0%)	2 (8.7%)
Stage IIIB	118 (20.5%)	14 (15.6%)	99 (21.4%)	5 (21.7%)
Stage IV	420 (73.0%)	71 (78.9%)	333 (72.1%)	16 (69.6%)
Unknown	3 (0.5%)	-	3 (0.6%)	-
Age at initial diagnosis (years) [mean (SD); median (range)]**	64.6 (10.0); 65.0 (35.8-86.8)	64.2 (11.6); 64.5 (35.8-83.8)	64.7 (9.8); 65.2 (37.4-86.8)	63.0 (8.5); 64.2 (44.2-76.0)
Time elapsed from initial diagnosis to enrollment (months) [mean (SD); median (range)]**	5.1 (11.6); 1.8 (0.1-141.8)	4.8 (8.4); 1.5 (0.1-49.4)	5.2 (12.3); 1.8 (0.1-141.8)	5.3 (7.5); 2.5 (0.5-34.8)
Metastatic sites at initial diagnosis (n, %)*				
Bone	179 (31.1%)	34 (37.8%)	137 (29.6%)	8 (34.8%)
Brain	102 (17.7%)	10 (11.1%)	88 (19.0%)	4 (17.4%)
Adrenal glands	63 (11.0%)	3 (3.3%)	58 (12.6%)	2 (8.7%)
Liver	56 (9.7%)	10 (11.1%)	45 (9.7%)	1 (4.3%)
Pleura/pleural effusion	49 (8.5%)	11 (12.2%)	34 (7.4%)	4 (17.4%)
Both lungs	32 (5.6%)	14 (15.6%)	15 (3.2%)	3 (13.0%)

*Only those reported in at least 10% of one of the populations have been presented. **Missing data in one patient with EGFR M–.

The *EGFR* mutation status was positive in 15.7% (90/575) (95%CI=12.7-18.6), negative in 80.3% (462/575) (95%CI=77.1-83.6), and not evaluable (EGFR Mx) in the remaining 4.0% (23/575) (95%CI=2.4-5.6) of the patients. Simple logistic regression analysis did not demonstrate a statistically significant association between adenocarcinoma tumor histology and *EGFR* mutation status; on the other hand, smokers (current or former smokers) were less likely than never smokers (odds ratio (OR)=0.10; 95%CI=0.06-0.17; $p<0.001$), and males were less likely than females (OR=0.20; 95%CI=0.12-0.32; $p<0.001$) to harbor *EGFR* mutations. Multiple logistic regression model including gender, smoking status and adenocarcinoma histology, confirmed the above findings with males and smokers shown to be less likely to be

Table II. *Frequency of EGFR mutations in exons 18-21: EGFR M+ subpopulation.*

EGFR M+ (N[a]=89)	n	%
Exon 18	2	2.2
G719A	1	1.1
Other than G719C or G719S	1	1.1
Exon 19	53	59.6
Del E746_A750	21	23.6
Del L747_A750>P	2	2.2
Del L747_T751	2	2.2
Del E746_S752>V	1	1.1
Del E746_T751>A	1	1.1
Del L747_E749	1	1.1
Other	8	9.0
Unspecified	17	19.1
Exon 20	10	11.2
Other than T790M, S768I or D770_N771 (ins NPG), D770_N771 (ins SVQ), D770_N771 (ins G)	5	5.6
Deletions other than D770_N771 (ins NPG), D770_N771 (ins SVQ), D770_N771 (ins G)	2	2.2
pQ787Q polymorphism	1	1.1
Unspecified	2	2.2
Exon 21	26	29.2
L858R	23	25.8
Other than L861Q	2	2.2
Unspecified	1	1.1

[a]Total number of patients with available data pertaining to the type of *EGFR* mutation.

EGFR M+ than *EGFR* M– ($OR_{adjusted}$=0.68; 95%CI=0.51-0.90; p=0.008; and $OR_{adjusted}$=0.40; 95%CI=0.30-0.53; p<0.001, respectively), and adenocarcinoma histology was not shown to be a predictive factor of EGFR mutation positivity ($OR_{adjusted}$=0.95; 95% CI=0.67-1.33; p=0.751).

EGFR mutation status screening and detection. The tissue sample for *EGFR* mutation testing had originated from the primary tumor for 85.2% (490/575) of the patients, and from a metastatic lesion in the remaining 14.8% (85/575). In the overall population, direct sequencing had been employed as the *EGFR* detection method in 69.0% (397/575), followed by high-resolution melt analysis (HRMA) in 13.0% (75/575), targeted methods (such as an amplification refractory mutation system (ARMS); cobas® and TheraScreen®) in 12.2% (75/575), polymerase chain reaction (PCR) in 10.6% (61/575) and pyrosequencing in 3.1% (18/575),while the method was unknown in 9.9% (57/575). Notably, for 61.7% (355/575) direct sequencing had been used without any targeted method, while in 7.3% (42/575) both direct sequencing and a targeted method had been employed. In the *EGFR* M+ subpopulation, direct sequencing had been used in 64.4% (58/90), HRMA in 14.4% (13/90); targeted methods in 13.3% (12/90); PCR in 11.1% (10/90); pyrosequencing in 5.6% (5/90); the method was unknown in 14.4% (13/90). The most prevalent *EGFR* mutation site was exon 19 (59.6%; 53/89), followed by exon 21 (29.2%; 26/89) (Table II).

First-line treatment patterns. In the eligible patient population (PP; N=564), first line treatment had been initiated at a median of 0.8 (interquartile range (IQR)=0.4-1.4) months following histological confirmation of disease diagnosis for the *EGFR* M+, a median of 1.0 (IQR=0.5-1.8) month for the *EGFR* M-subpopulation, and 1.7 (IQR=0.9-3.4) months for the *EGFR* Mx. The most common first-line treatment pattern in the patient subpopulations per *EGFR* mutation status were: EGFR-TKI monotherapy (67.0%; 59/88) for the *EGFR* M+ population; and multi-agent chemotherapy in both the *EGFR* M– (61.7%; 280/454) and *EGFR* Mx subpopulations (86.4%; 19/22) (Figure 3A). The three most commonly prescribed agents were gefitinib (47.7%; 42/88), carboplatin (28.4%; 25/88), and erlotinib (19.3%; 17/88) in the *EGFR* M+ subpopulation; carboplatin (64.5%; 293/454), pemetrexed (39.0%; 177/454), and bevacizumab (27.8%; 126/454) in the *EGFR* M– subpopulation. The first line treatment patterns in the overall population per ECOG performance status are displayed in Figure 3B. Of the *EGFR* M+ patients, 68.6% (24/35) of those with PS0, 64.6% (31/48) with PS1, 75.0% (3/4) with PS2, and the single patient with PS3 received EGFR-TKI containing therapy.

Clinical response to therapy in the EGFR M+ subpopulation. Over a median 8.8 months (range=0.5-42.2 months) of exposure to first line treatment, the Kaplan-Meier estimated that the median PFS time in the eligible *EGFR* M+ population (n=88) was 9.67 (95%CI=7.90-11.77) months (Figure 4). A Cox multivariable proportional hazards model (n=86) was used to examine the association of factors of interest withthe PFS. Presence *versus* absence of bone and/or brain metastasis at initial diagnosis was shown to confer a higher risk of disease progression (HR=1.93; 95%CI=1.16-3.22; p=0.011), while presence *versus* absence of exon 19 *EGFR* mutation a lower risk of disease progression (HR=0.56; 95%CI=0.32-0.97; p=0.040). On the other hand, age (>65 *versus* ≤65 years) at initial NSCLC diagnosis (HR=0.71; 95%CI=0.42-1.20; p=0.200); smoking status (never smoker *versus* smoker) (HR=1.05; 95%CI=0.62-1.76; p=0.866); and non-adenocarcinoma histology at initial diagnosis (*versus* adenocarcinoma histological type) (HR=0.63; 95%CI=0.30-1.31; p=0.215) were not shown to be associated with PFS. During the study observation period (median of 6.9 months; range=0.03-43.7 months), a total of 12 deaths (13.6%) were reported; the Kaplan-Meier median OS time was not estimable due to data immaturity. The DCR among eligible *EGFR* M+ patients with available clinical response data (n=80) was 67.5% (95%CI=57.2-77.8).

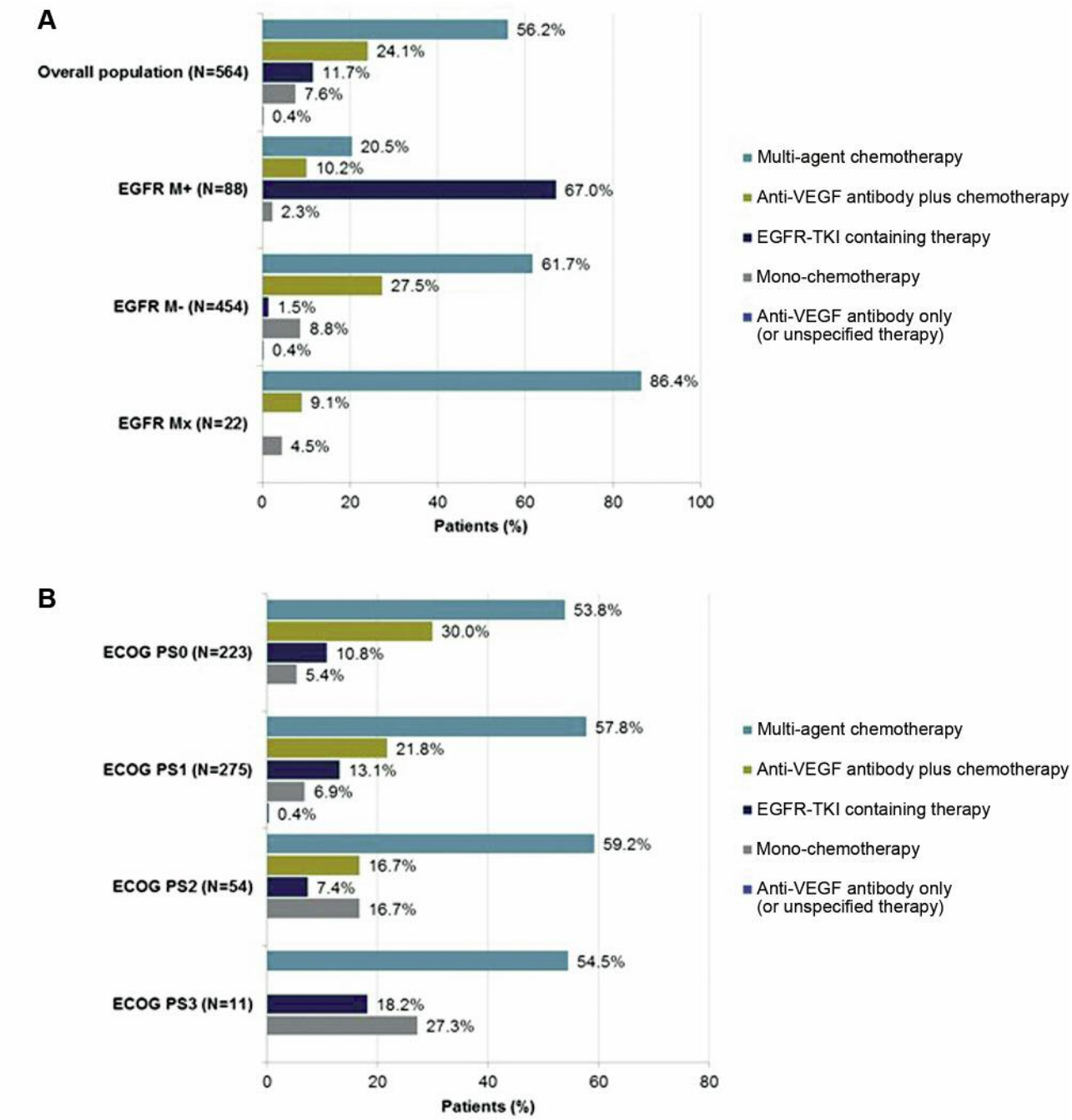
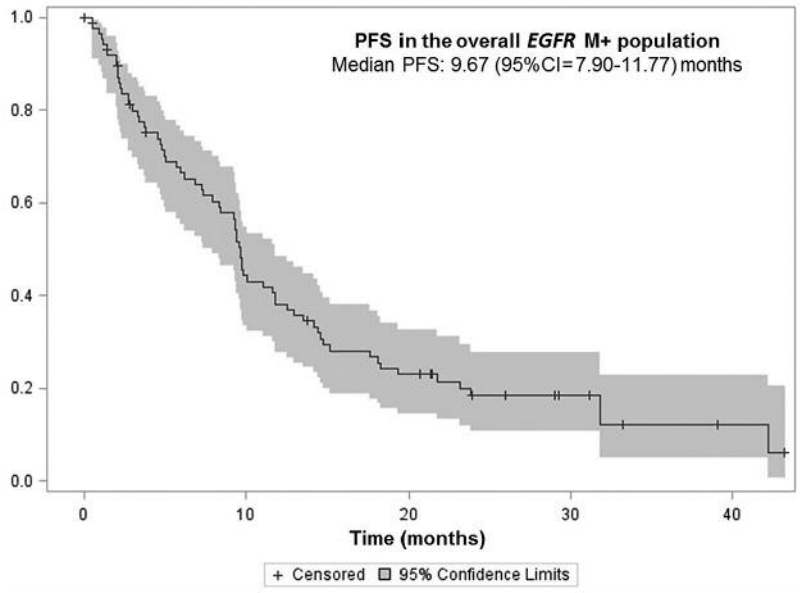


Figure 3. *First-line treatment patterns at enrollment by treatment categories (A) in the overall eligible patient population and subpopulations by EGFR mutation status and (B) by ECOG performance status at enrollment.*

Healthcare resource utilization in the EGFR M+ subpopulation. Over a cumulative post-enrollment study observation period of 73.4 years, a total of 102 hospitalizations (median: 2.0; IQR=1.0-3.5) were reported for 32/82 (39.0%) of the eligible *EGFR* M+ patients with available data, yielding a hospitalization incidence rate of 1.39 per person-year. Similarly, a total of 244 outpatient visits (median: 4.0; IQR=1.0-5.0) were reported for 50/82 (61.0%) of the *EGFR* M+ patients, yielding an outpatient visit incidence rate of 3.32 per person-year.



Time (months)	0	10	20	30	40
Persons at risk	88	36	18	7	2
Number censored	0	6	7	15	18

Figure 4. *Kaplan–Meier progression-free survival plot in the eligible EGFR M+ population.*

Discussion

The Greek REASON represents the widest epidemiological dataset of clinicopathological characteristics, treatment patterns and outcomes in Caucasian patients with advanced NSCLC treated in the routine care of Greece. In our study, 15.7% of the patients had an *EGFR* M+ status matching the 15.8% rate reported in another Greek study of approximately 1,500 NSCLC patients (21). On the other hand, the respective frequency was 10.3% in the German REASON (18), 11.6% in the Spanish REASON (19), while other studies conducted in Caucasian populations have reported frequencies ranging from 13.6% to 16.6% (15-17, 20). Variance in reported *EGFR* mutation prevalence rates may undoubtedly lie in inter-ethnic variations as outlined in the study's rationale, but also in inter-assay variations, underscoring the importance of precise referencing the *EGFR* mutational testing methods utilized (21, 22).

In uniformity to the German (18) and Spanish (19) REASON studies, the study population of the Greek REASON was mainly comprised of males and smokers (current or former), diagnosed with stage IV adenocarcinoma and with an ECOG PS of 0 or 1. Males represented 62% of the enrolled population in the German REASON and roughly 73% in the Spanish and Greek REASON; smokers comprised about 82% of the population in all three studies, while adenocarcinoma histology was reported in 58%, 69% and 81% of the Spanish, German and Greek REASON studies, respectively. In our study, an *EGFR* positive mutation status was identified in 9.2% of the male population, but in 33.3% of the females; in 8.6% of smokers but in 49.0% of never smokers; and in 16.4% of patients with adenocarcinoma *versus* 12.2% of those with non-adenocarcinoma. These trends are not dissimilar from those reported elsewhere (17-21). In particular, the reported mutation frequencies in the Spanish REASON,German REASON and the recent Greek observational study ranged from 6.4-11.7% in males and from 16.7-25.4% among females; from 6.4-11.5% in smokers and 25.6-38.1% in never smokers; and from 13.1-16.6% in adenocarcinomas to 3.8-11.5% in non-adenocarcinomas (18, 19, 21).

According to a multiple logistic regression model controlling for gender, smoking status, and histological type, males and smokers had decreased odds of harboring an *EGFR* mutation than females and never smokers, respectively, in alignment with the relative frequencies reported above. However, on the other hand, according to the model, adenocarcinoma histologic type was not found to be

associated with an *EGFR* M+ status, despite the higher *EGFR* mutation frequency noted among patients with adenocarcinomas. The Spanish REASON study reported the same finding; however, the German REASON, in addition to females and never smokers, also demonstrated that adenocarcinoma histology increases the odds of harboring an *EGFR* mutation (18, 19).

More than 89% of the *EGFR* M- patients received first line multi-agent chemotherapy or combination chemotherapy with anti-VEGF antibody, in alignment with the contemporary ESMO guidelines recommending chemotherapy with platinum doublets, platinum-based chemotherapy with any third-generation cytotoxics, or platinum-based chemotherapy with bevacizumab as the first-line treatment options for this NSCLC population. On the other hand, approximately 33% of the patients with an EGFR M+ status were managed with first line treatment patterns which did not contain EGFR-TKIs, the guideline-recommended first line treatment option for this patient population (6, 7). Recording of the factors guiding the treatment decision-making was beyond the scope of the study, thus not allowing the reasoning for this divergence between the guideline recommendations and clinical practice to be deciphered. Nevertheless, it becomes apparent that there are still opportunities to enhance adoption of evidence-based personalized strategies in the routine care of Greece aiming at further improving the clinical outcomes in this difficult-to-treat population.

Median PFS in the *EGFR* M+ population was estimated to be 9.67 (95%CI=7.90-11.77) months with approximately 67% of this population comprised of patients receiving first line EGFR-TKI containing therapy. A similar PFS (10.8 (95%CI=4.8-15.3) months)was reported in the Galician Lung Cancer Group observational study, in which 88% of the patients had received EGFR-TKI containing therapy (19), but also in the open-label phase IV IFUM study (median PFS 9.7 (95%CI=8.5-11.0)) months)of 118 Caucasian *EGFR* mutation positive stage III/IV patients (15). A clear benefit of EGFR-TKIs *versus* chemotherapy in the first line setting of *EGFR* M+ patients has been demonstrated in many randomized controlled trials (RCTs), with PFS ranging from 8 to 13.1 months with EGFR-TKIs *versus* 4.6-6.7 months with chemotherapy (23). The advantage conferred by EGFR-TKIs over chemotherapy, including not only on PFS, but also on OS and DCR, have been demonstrated in several meta-analyses of RCT data (24-27), leading to their establishment as the optimal first line treatment option for patient with *EGFR* mutation positive advanced NSCLC (6-8).

Regarding the identification of factors of poor prognosis in advanced *EGFR* M+ NSCLC, in our study, patients with bone and/or brain metastases were shown to have an approximately double risk of disease progression, while those with an exon 19 *EGFR* mutation were identified to have a lower risk of disease progression. Worse outcomes among *EGFR* M+ patients with brain metastases as well as in those with mutations other than exon 19 deletions have been previously reported (28, 29).

The inherent strength of the study's design, aiming to capture data under real-life clinical practice, and thus not mandating the employment of specific *EGFR* mutation screening methods or specific response criteria (*e.g.* RECIST), has generated limitations in the respective outcomes stemming from inter-assay and/or inter-observer variations. Furthermore, as certain study outcomes involve a relative limited number of available observations, caution should be exercised when interpretingthe statistical significance of these study outcomes. Lastly, as it pertains to the *EGFR* M+ subpopulation, the lack of post-withdrawal survival data collection and the short on-study observation period (median 6.9 months) have likely contributed to the inability to generate overall survival estimates.

Nonetheless, this study yielded real-world data on a patient population whose epidemiological data, long-term outcomes and treatment practice paradigms employed in Greece are understudied. It is anticipated that study outcomes may help optimize diagnostic algorithms and augment personalized management with targeted treatment options in the routine care of advanced NSCLC.

Conflicts of Interest

Prof. K.S declared no conflict of interst, Prof. V.G. has received speaker honorarium from MSD, Astra Zeneca and Novartis, Prof. K.Z. declared no conflict of interest, Dr P.M.has received a speaker honorarium from BMS, Novartis, Roche, Dr A.C. has received Honoraria from Brisol Mayer Squib, Pfizer, Roche Genetech and ASTRA Zeneca and Consultation fees from Boehringer Ingelheim, Dr C.C. have participated in advisory board and / or have received speaker honorarium from: Novartis, Roche, BMS, MSD, Amgen, Astra Zeneca, Pfizer, Merck, Genesis.

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