Treating *EGFR*-Mutated Oncogene-Addicted Advanced Non–Small-Cell Lung Cancer in the Era of Economic Crisis in Greece: Challenges and Opportunities

Purpose Because of the profound financial crisis that commenced in Greece in 2010, severe cuts in health care spending and other restriction measures led to significant delays in the reimbursement of novel antineoplastic agents. In 2011, the Hellenic Society of Medical Oncology initiated a program of early access to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors for the treatment of patients with advanced, *EGFR*-mutant non–small-cell lung cancer (NSCLC). We evaluated treatment patterns and clinical outcomes in patients with *EGFR*-mutant or wild-type disease treated at a large center in Greece throughout the period of financial crisis.

Patients and Methods From 2011 through 2015, 252 patients with newly diagnosed advanced NSCLC were treated at the Department of Medical Oncology of the Papageorgiou Hospital, a tertiary cancer center in northern Greece. We retrospectively reviewed patient medical records to obtain clinicopathologic characteristics, *EGFR* mutation status, and follow-up data. The primary end point was time to treatment failure.

Results Of the 198 evaluable patients, 25 (12%) had *EGFR* mutations. All patients with *EGFR* mutations except one received treatment with an EGFR tyrosine kinase inhibitor. Median times to treatment failure for patients with *EGFR*-mutant and wild-type disease were 15.8 and 7.1 months, respectively (hazard ratio, 0.58; 95% CI, 0.35 to 0.95; *P* = .031). There was no difference in overall survival between the two groups (*P* = .293). No deviation from treatment guidelines or discontinuation of treatment regimens occurred because of logistic reasons or drug shortages.

Conclusion Despite restrictions in the reimbursement policy and accompanying controls in the use of high-cost medicines, the national program enabled treatment of patients with *EGFR*-mutant NSCLC according to established guidelines. Therefore, the clinical outcomes of such patients treated in Greece during the economic crisis were in accordance with international standards.

Elena Fountzilas

Sofia Levva

Giannis Mountzios

Genovefa Polychronidou

Nikos Maniadakis

Vassiliki Kotoula

George Fountzilas

Author affiliations and support information (if applicable) appear at the end of this article.

E.F. and S.L. have equally contributed to this work.

Corresponding author: Elena Fountzilas, MD, PhD, Department of Investigational Cancer Therapeutics, The University of Texas, MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX, 77030; e-mail: fountzila@oncogenome.gr.

INTRODUCTION

Lung cancer remains a prominent public health care issue; it is the leading cause of cancer mortality worldwide.[1,2] Non–small-cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancer cases.[3] The incidence of its two main histopathologic subtypes has changed during the last years, following the evolution of smoking habits in both sexes. In men, the incidence of squamous cell carcinoma has decreased, whereas the incidence of adenocarcinoma has increased in both the United States and Europe. In women, the same trends have been observed in the United States; however, in Europe, the incidence of both histologic subtypes has increased.[4]

Genotyping studies have revealed molecular abnormalities in NSCLC, resulting in changes in patient management. Activating epidermal growth factor receptor (*EGFR*) mutations are found in approximately 10% to 15% of whites with lung adenocarcinoma and are more frequent in never-smokers, women, and those of East Asian ethnicity. *EGFR* mutations predict benefit from EGFR tyrosine kinase inhibitors (TKIs)[5-7]; specifically, EGFR TKIs confer significantly improved progression-free survival (PFS) compared with standard platinum-based chemotherapy in patients with *EGFR* mutations.[8,9]

The EGFR TKIs have become the treatment of choice for patients with advanced, *EGFR*-mutant NSCLC in the first-line setting, recommended by European Society for Medical Oncology guidelines with level I evidence since 2011,[10] whereas chemotherapy has remained the gold standard for patients with tumors without targetable genetic alterations.[11] The advent of immunotherapy has dramatically changed the treatment landscape; however, its actual place in the treatment algorithm remains to be elucidated.

The implementation of novel therapeutic strategies against NSCLC, such as molecular targeted agents and immunotherapy, has substantially increased the costs related to cancer care and challenged the reimbursement capacity of health care systems, especially in countries with weak economies. Greece is such a country; it entered a profound financial crisis in 2010, which has continued to date, and has been forced to follow a strict rescue program with unprecedented reforms and expense restrictions, including major cuts in health care and pharmaceutical costs. On the fiscal side, Greece has experienced as a result of the restriction policies the largest annual average reduction in health care and pharmaceutical expenditures of all countries in the Organisation for Economic Co-operation and Development.[12] Of note, in this context, gefitinib, the first EGFR TKI to gain European Medicines Agency (EMA) approval, in July 2009, became refundable in Greece almost 5 years later, in 2014. To tackle this issue and assess the impact of the aforementioned trends, we performed a retrospective, observational, single-institute study in a tertiary cancer center to describe and analyze treatment patterns and clinical outcomes in Greek patients diagnosed with advanced NSCL, during the period of economic crisis, with a special focus on those with *EGFR* mutations.

PATIENTS AND METHODS

Patient Characteristics

We studied patients with newly diagnosed advanced NSCLC treated from January 2011 through December 2015 at the Department of Medical Oncology, Papageorgiou Hospital, in the Aristotle University School of Medicine (AUTH) in Thessaloniki, which covers a large area of northern Greece. We retrospectively reviewed patient medical records to obtain clinicopathologic characteristics, *EGFR* mutation status, and outcome data. Informed consent had been obtained at the time of diagnosis from all patients for the use of their medical records and biologic material for research purposes. All procedures were performed according to the principles of the Declaration of Helsinki and were approved by the ethics committee of the AUTH (A13064; July 16, 2010) and the scientific committee of the Hellenic Cooperative Oncology Group.

EGFR Status Assessment

Tumor tissue (formalin fixed, paraffin embedded) and/or cytologic (cell block) material was obtained at the time of diagnosis from either the primary tumor or a metastatic site, depending on availability. Molecular testing was performed in laboratories internationally certified for *EGFR* mutation testing; 70% of the tumors were analyzed in the AUTH Department of Pathology or Hellenic Foundation for Cancer Research/Hellenic Cooperative Oncology Group Laboratory of Molecular Oncology, and 30% were analyzed in private laboratories, as previously described.[13] Details are provided in the Data Supplement.

Statistical Analyses

Categorical data were assessed using THE χ^2 test, and continuous data were assessed with the nonparametric Mann-Whitney test. The primary end point of the study was time to treatment failure (TTF), defined as time in months from first-line treatment initiation to the date of radiographically or clinically observed disease progression. PFS was defined as time in months from first-line treatment initiation to the date of radiographically or clinically observed disease progression or death, whichever occurred first. Overall survival (OS) was defined as time in months from the date of initiation of treatment for metastatic NSCLC to the date of patient death or last contact. Patients alive were censored at the date of last contact. Kaplan-Meier curves and log-rank tests were used to compare survival distributions between groups of patients. Cox multivariable analysis was performed to identify independent variables associated with survival. Statistical significance was set at two-sided $P = .05$. Statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows [version 24.0]; IBM, Armonk, NY).
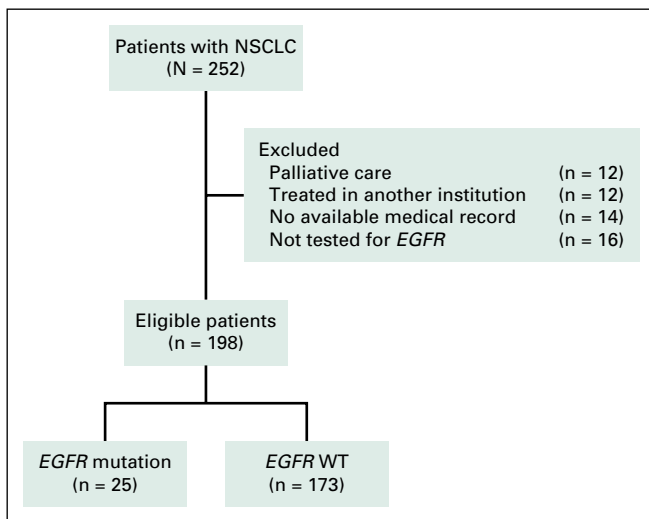
Fig 1. CONSORT diagram. NSCLC, non–small-cell lung cancer; WT, wild type.

Patients with NSCLC
(N = 252)

Excluded
Palliative care   (n = 12)
Treated in another institution   (n = 12)
No available medical record   (n = 14)
Not tested for *EGFR*   (n = 16)

Eligible patients
(n = 198)

EGFR mutation
(n = 25)

EGFR WT
(n = 173)

RESULTS

Patient Characteristics

From January 2011 to December 2015, 252 patients were diagnosed with advanced NSCLC, of whom 228 (90.5%) received first-line treatment. Because of poor performance status and advanced disease, 12 patients received supportive care, whereas another 12 chose to be treated elsewhere. *EGFR* status was not available for 30 patients (lack of *EGFR* testing or medical record data; Fig 1).

Patient clinical characteristics are listed in Table 1. Our study included 198 evaluable patients, 151 of whom were men; median age was 65 years. Twenty-five (12.6%) of the patient tumors harbored an *EGFR* mutation in exons 18 to 21. The most common mutation was p.E746_A750delELREA in exon 19 (44%), followed by the p.L858R point mutation in exon 21 (28%). The distribution and annotations of the identified mutations are shown in Figure 2.

Patients with *EGFR* mutations were more likely to be women (64% v 18%; χ^2 $P <$ .001) and nonsmokers (48% v 7%; χ^2 $P <$ .001) compared with patients without *EGFR* mutations (*EGFR* wild type [WT]). They were also more likely to be diagnosed with lung adenocarcinoma (92% v 58%; χ^2 $P =$ .004). Performance status (PS) did not differ between patients with *EGFR* mutations versus WT (χ^2 $P =$ .052). Both groups received a median of two chemotherapy lines, with 15% of patients receiving ≥ four lines of treatment.

Treatments

All patients with *EGFR* mutations except three received an EGFR TKI as first-line treatment. Two patients who were initially treated with chemotherapy based on physician's choice received an EGFR TKI after disease progression, for 3 (p.N771>GY, exon 20) and 24 months (L858R, exon 21), respectively. The third patient died before he could receive any additional treatment. Overall, 15 patients received treatment with gefitinib, five with erlotinib, and four with afatinib. Circulating tumor cell–free DNA analysis (liquid biopsy) was performed in four patients, two of whom tested positive for the T790M mutation. The tumors of both of these patients initially harbored a deletion in exon 19.

Among *EGFR* WT patients, 98% received platinum-based doublet chemotherapy in the first-line setting. Twelve patients received immunotherapy with an anti–programmed death 1 (PD1) checkpoint inhibitor as a subsequent therapy line, following pertinent EMA approvals. Notably, all patients received treatment until disease progression or unacceptable toxicity, whichever came first, and no treatment discontinuation occurred because of logistic reasons or drug shortages.

Patient Outcomes

Median follow-up for all patients in our study was 27 months. As expected, patients with good PS (0 or 1) had significantly increased OS, compared with patients with poor PS (≥ 2; hazard ratio [HR], 0.43; 95% CI, 0.26 to 0.72; $P =$ .001; Figs 3A and 3B). TTF was longer for patients with good versus poor PS, but not at a statistically significant level (HR, 0.64; 95% CI, 0.40 to 1.03; $P =$ .064). In univariable analysis, women had increased OS compared with men (HR, 0.62; 95% CI, 0.40 to 0.97; $P =$ .038), but there was no difference in TTF between the two sexes. There was a trend toward increased OS and TTF for nonsmokers compared with smokers (HR, 0.53; 95% CI, 0.28 to 1.01; $P =$ .055 and HR, 0.58; 95% CI, 0.33 to 1.00; $P =$ .051, respectively). There was no significant difference in TTF (HR, 1.10; 95% CI, 0.93 to 1.30; $P =$ .231) or OS (HR, 1.09; 95% CI, 0.90 to 1.34; $P =$ .375) between *EGFR* WT patients who received different platinum doublets (Figs 3C and 3D). Bevacizumab was part of first-line treatment in

Table 1. Patient Demographic and Clinicopathologic Characteristics

Characteristic	EGFR Mutation (n = 25) No.	EGFR Mutation (n = 25) %	EGFR WT (n = 173) No.	EGFR WT (n = 173) %	P
Age, years					.216
Mean ± SD	66 ± 11.4		63.7 ± 9.4		
Median	65		65		
Range	40-81		39-87		
Sex					**< .001**
Female	16	64	31	18	
Male	9	24	142	82	
Histologic subtype					**.004**
Adenocarcinoma	23	92	100	58	
Squamous	1	4	60	35	
Large cell	1	4	2	1	
Other			11	6	
Smoking status					**< .001**
Yes	11	48	127	93	
No	12	52	10	7	
Missing	2		36		
PS					.052
0	9	53	55	38	
1	3	17	62	43	
2	2	12	21	15	
3	2	12	4	3	
4	1	6	1	1	
Missing	8		30		
Bone-only metastasis					.100
Yes	1	4	24	15	
No	24	96	141	85	
Missing			8		
Brain metastasis					.058
Yes	10	42	44	26	
No	14	58	127	74	
Missing	1		2		
First-line treatment regimen					NA
Platinum + paclitaxel			19	12	
Platinum + docetaxel	1	4	75	47	
Platinum + pemetrexed	2	8	38	24	
Platinum + gemcitabine			23	15	
Pemetrexed			1	0.5	
Carboplatin					
Paclitaxel			2	1	
Docetaxel			1	0.5	
+ Bevacizumab			32	19	
Gefitinib	15	60			
Erlotinib	3	12			

(Continued on following page)

Characteristic	EGFR Mutation (n = 25)		EGFR WT (n = 173)		P
	No.	%	No.	%	
Afatinib	4	16			
Missing			14		
No. of treatments					.442
Mean ± SD	2.2 ± 1.5		2.2 ± 1.2		
Median	2		2		
Range	1-6		1-8		

NOTE. Bold font indicates significance.
Abbreviations: NA, not applicable; PS, performance status; SD, standard deviation; WT, wild type.

19% of patients. The addition of bevacizumab to first-line treatment resulted in improved TTF (HR, 0.64; 95% CI, 0.41 to 0.98; P = .042; Figs 3E and 3F) and a trend toward improved OS (HR, 0.64; 95% CI, 0.38 to 1.06; P = .084; Fig 3E and 3F). Median TTF and OS of patients who received immunotherapy as part of later treatment lines were 8 months and not yet reached, respectively.

Regarding patients with and without oncogene-addicted NSCLC, we recorded 102 deaths among *EGFR* WT patients and 18 among those with *EGFR* mutations. Median TTF for those with *EGFR* mutations versus WT was 15.8 versus 7.1 months, respectively (HR, 0.58; 95% CI, 0.35 to 0.95; P = .031; Fig 4). Median PFS of those with *EGFR* mutations was also improved compared with *EGFR* WT patients (15.8 v 6.7 months, respectively; HR, 0.53; 95% CI, 0.33 to 0.87; P = .013; Fig 4). There was no significant difference in OS between the two groups (HR, 0.76; 95% CI, 0.46 to 1.27; P = .293; Fig 4). There was no difference in either OS (P = .337)

or TTF (P = .560) between patients with *EGFR* mutations and WT patients with brain metastases. In a multivariable model encompassing PS (the only parameter associated with TTF in our patient cohort), *EGFR* status maintained its prognostic significance (HR, 0.51; 95% CI, 0.28 to 0.92; P = .025).
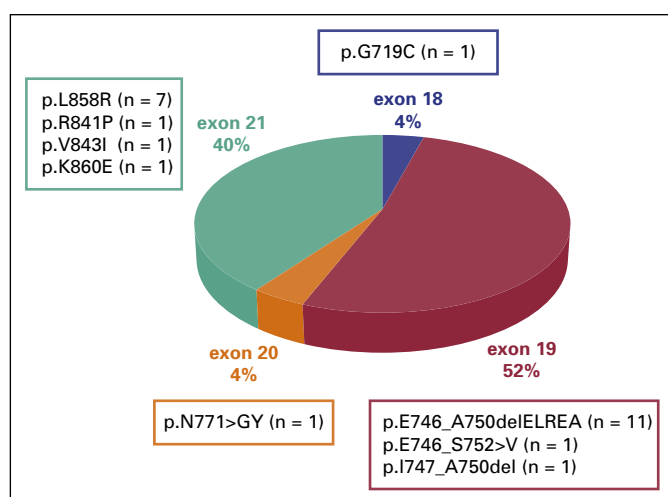
We did not identify any difference in survival outcomes between patients with tumors harboring *EGFR* exon 19 mutations versus patients with tumors with the exon 21 substitution mutation (TTF: HR, 1.07; 95% CI, 0.64 to 1.82; P = .789; OS: HR, 1.10; 95% CI, 0.65 to 1.86; P = .720). Two patients with exon 19, one with exon 21, and one with exon 18 *EGFR* mutations received afatinib. Because of the small number of patients, we did not address EGFR TKI efficiency.

DISCUSSION

This was a single-institute retrospective observational study of patients with newly diagnosed advanced NSCLC. To our knowledge, this is the first study reporting clinical outcomes in correlation with treatment regimens in Greek patients with oncogene-addicted NSCLC in the era of the financial crisis. We found that Greek patients with *EGFR*-mutant tumors diagnosed during this period had clinical outcomes consistent with those in other parts of the world reported in the literature.[14-17]

In 2010, Greece entered a deep economic crisis, which led to significant reduction in gross domestic product, coupled with large deficits and public debts. Significant deformities in the economy, public sector, and government made it impossible to borrow money from the international markets. Hence, in May 2010, the European Commission, European Central Bank, and

Fig 2. *EGFR* mutation distribution. Thirteen (52%) *EGFR* mutations were in frame deletions, 11 (44%) were substitutions, and one was an insertion (4%).
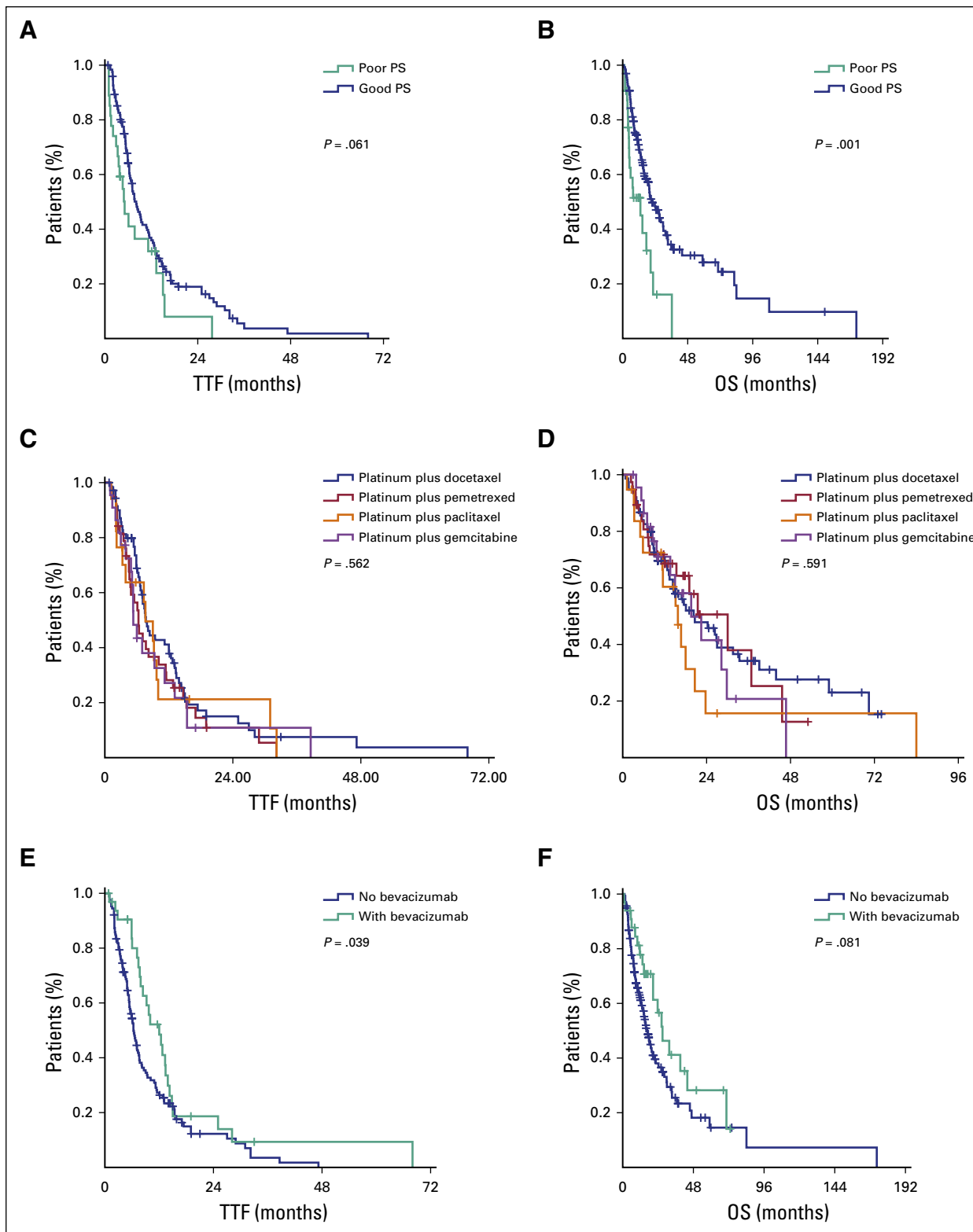

p.G719C (n = 1)

p.L858R (n = 7)
p.R841P (n = 1)
p.V843I (n = 1)
p.K860E (n = 1)

exon 21 40%

exon 18 4%

exon 20 4%

exon 19 52%

p.N771>GY (n = 1)

p.E746_A750delELREA (n = 11)
p.E746_S752>V (n = 1)
p.I747_A750del (n = 1)

Fig 3. Patient outcomes. (A) Time to treatment failure (TTF) and (B) overall survival (OS) in patients with good and poor PS. (C) TTF and (D) OS in *EGFR* wild-type (WT) patients receiving different first-line platinum-based treatment regimens. (E) TTF and (F) OS in *EGFR* WT patients treated with platinum-based first-line therapy with or without bevacizumab. + indicates censored patients.
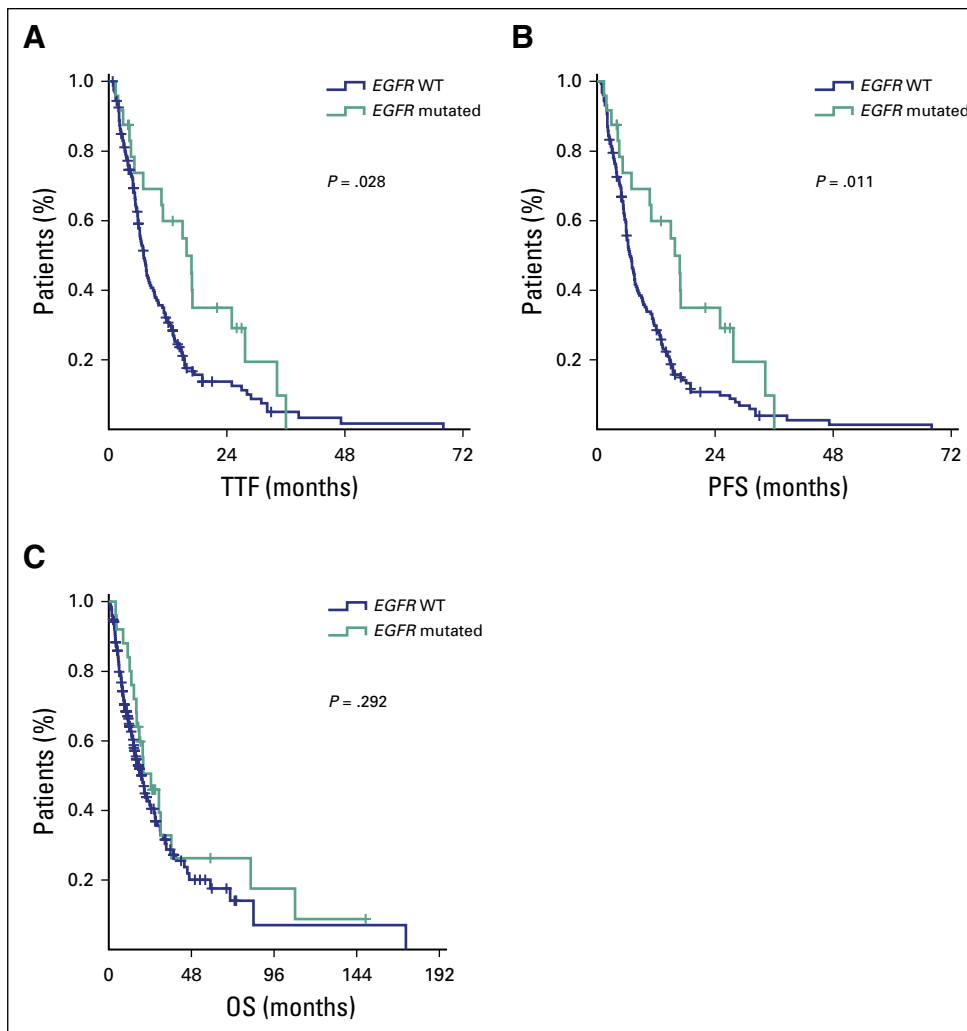
Fig 4. Patient outcomes in patients with *EGFR* mutations and *EGFR* WT patients: (A) time to treatment failure (TTF), (B) progression-free survival (PFS), and (C) overall survival (OS). + indicates censored patients.

International Monetary Fund, colloquially called the European troika, agreed with the Greek government to a 3-year financial aid program, outlined in a memorandum of understanding, which was subsequently extended with two additional programs ending in mid 2018.[18,19] Greece agreed to undertake unprecedented reforms in health and pharmaceutical care sectors. Specifically, three stability programs were implemented from May 2010 to August 2018 to attain fiscal and structural reforms. One of the major areas of intervention was health care, where the reforms were aimed at rationalizing expenditure and modernizing the system. As a result, an unprecedented reform program was implemented in health service provision, pharmaceuticals, primary care, public health care insurance, and financing. Rationalization of pharmaceuticals was attempted through development of an e-prescription system, prospective and retrospective physician prescription controls, prescription restrictions

with prior authorizations, protocol implementation, compulsory prescription by international nonproprietary name, positive and negative reimbursement lists, fixed budgets, external and internal reference systems, generic penetration support, negotiations, compulsory discounts, rebates, claw backs, and health technology assessment. During the 3-year period after the commencement of crisis, there was a freeze in the introduction of new products, followed by gradual controlled introduction thereafter. These reforms led to the largest reduction in health and pharmaceutical care spending among Organisation for Economic Co-operation and Development countries.[12]

Because of economic restrictions, even though EGFR TKIs had received EMA approval and have represented the treatment of choice for patients with *EGFR*-mutant advanced NSCLC since 2011,[10] they were not reimbursable in Greece
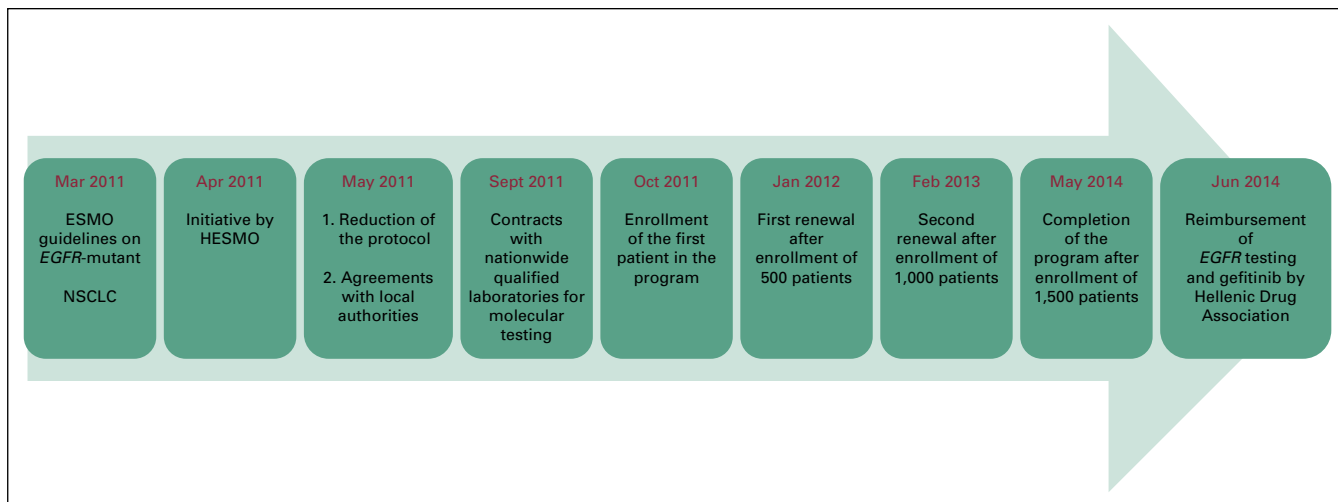
Fig 5. Timeline of the initiative undertaken by the Hellenic Society for Medical Oncology (HES-MO) to confront shortage of epidermal growth factor receptor tyrosine kinase inhibitors during the period of financial crisis in Greece. ESMO, European Society for Medical Oncology.

until 2014. In light of their profound clinical benefit and to confront the drug shortage, in 2011, the Hellenic Society of Medical Oncology (HESMO) undertook the initiative to organize a program of early access to these drugs in conjunction with the label-owning pharmaceutical companies. To this purpose, HESMO collaborated with the Hellenic Drug Administration, Greek Ministry of Health, and Hellenic Association of Pharmaceutical Companies, as well as with public and private laboratories performing certified molecular testing, to elaborate on an early-access program that included both free *EGFR* testing and access to the three available EGFR TKIs: erlotinib, gefitinib, and afatinib. The timeline of this initiative is presented in Figure 5. The initial program included free testing for 500 patients but was renewed twice, in January 2012 and February 2013, resulting in 1,500 patients registered until 2014, when reimbursement for EGFR TKIs and *EGFR* testing was established in Greece. This initiative covered the needs of Greek patients during the first years of the financial crisis and ensured that all eligible patients had access to these pivotal and irreplaceable agents.

We identified *EGFR* mutations in 12.6% of the patients tested. These results are comparable to previously reported *EGFR* mutations in 10% to 15% of unselected white patients with advanced NSCLC.[20,21] In one systematic review, Greece was one of the countries with the lowest *EGFR* mutation frequency among patients with NSCLC (8%) compared with other European countries.[22] Others reported the presence of *EGFR* mutations in 15.8% of Greek patients with NSCLC.[23] In the nationwide initiative by the HESMO, the overall incidence of

EGFR mutations among the 1,500 patients was 10.1% (152 patients). This difference might be attributed to disparities in sample size and patient clinical characteristics or to adequacy of tissue material for molecular profiling, with the nationwide results probably being the most representative. A vast majority of the *EGFR* mutations were deletions in exon 19 and the L858R point mutations, as expected.[24] Two of the seven less-common mutations identified in our patients' tumors (exon 21 mutations p.V843I and p.K860E) were previously identified in Greek patients with lung cancer.[25]

Patients with *EGFR* mutations had improved TTF and PFS compared with *EGFR* WT patients, whereas OS was similar between the two groups, as previously reported for the white[15,26] and Asian populations.[14,16,17,27] Among patients with rare *EGFR* mutations (exon 21 p.R841P and p.K860E and exon 20 p.N771>GY), only the patient with the p.R841P mutation responded to the EGFR inhibitor. Probably because of the small number of patients with *EGFR* mutations, we did not identify any difference in survival outcomes between patients with exon 19 and 21 mutations, as previously reported.[28] Because a majority of patients were diagnosed and treated earlier than 2015, data regarding T790M mutation status beyond progression during treatment with TKIs were available in only four patients, through a program for free testing organized by HESMO. Of note, patients were treated before the era of third-generation EGFR TKIs. Availability of these drugs might have further improved patient outcomes.

In *EGFR* WT patients of our cohort, median OS was higher compared with reports in clinical trials

assessing standard first-line treatment regimens in advanced NSCLC.[29] These results may be attributed to newer therapeutic approaches, such as the addition of bevacizumab to chemotherapy and use of maintenance therapy after initial platinum doublet chemotherapy in the patients of our cohort.[30,31] Because of the small sample size, these results must be interpreted with caution.

We found a higher, although of borderline significance, incidence of brain metastases (BMs) in patients with *EGFR* mutations compared with WT. Published data on BM frequencies in patients with *EGFR* mutations and *EGFR* WT patients are contradictory.[32-36] A large meta-analysis incorporating 22 studies with 8,152 patients revealed that *EGFR* mutations were associated with a significantly higher incidence of BMs and that those with EGFR mutations who presented with BMs had a longer BM-related OS.[36]

There are several limitations to our study. The major drawbacks are the retrospective nature of the study and inclusion of patients from only one institution, leading to a small number of patients with *EGFR* mutations in the final analysis. These limitations did not allow the assessment of outcome differences between patients with *EGFR* mutations in different exons or between different EGFR inhibitors or according to mutation.

Our results suggest that despite the economic crisis and restrictions in reimbursement policy, patients with EGFR mutations received the appropriate EMA-approved treatment according to established international guidelines. Collaboration of HESMO with the Hellenic regulatory agencies and the Hellenic Association of Pharmaceutical Companies ensured that there would be no treatment deviations or discontinuation because of logistic or economic reasons. Therefore, clinical outcomes of Greek patients with *EGFR* mutations were similar to the expected outcomes. With the introduction of novel treatment agents (ie, third-generation EGFR inhibitors and anti-PD1/PD1 ligand checkpoint inhibitors), additional studies are warranted to reevaluate outcome differences between patients with and without *EGFR* mutations, taking into account both the efficacy of novel agents and increased pharmaceutical costs.

AUTHOR CONTRIBUTIONS:

Conception and design: Elena Fountzilas, Sofia Levva
Provision of study material or patients: Vassiliki Kotoula, George Fountzilas
Collection and assembly of data: Elena Fountzilas, Sofia Levva, Genovefa Polychronidou, Vassiliki Kotoula, George Fountzilas
Data analysis and interpretation: Elena Fountzilas, Sofia Levva, Giannis Mountzios, Nikos Maniadakis, Vassiliki Kotoula, George Fountzilas
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF
POTENTIAL CONFLICTS OF INTEREST

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Elena Fountzilas
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Consulting or Advisory Role: Pfizer (I), Sanofi (I), Roche (I)

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Genovefa Polychronidou
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Vassiliki Kotoula
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George Fountzilas
Honoraria: AstraZeneca
Consulting or Advisory Role: Pfizer, Roche, Sanofi

Affiliations

Elena Fountzilas, MD Anderson Cancer Center, The University of Texas, Houston, TX; **Sofia Levva** and **Genovefa Polychronidou**, Papageorgiou Hospital; **Sofia Levva**, **Genovefa Polychronidou**, and **Vassiliki Kotoula**, School of Health Sciences, Aristotle University of Thessaloniki; **Vassiliki Kotoula** and **George Fountzilas**, Hellenic Foundation for Cancer Research; **George Fountzilas**, Aristotle University of Thessaloniki, Thessaloniki; **Giannis Mountzios**, Henry Dunant Hospital Center; and **Nikos Maniadakis**, National School of Public Health, Athens, Greece.

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