

# An Observational Study to Assess the Molecular Epidemiology and Direct Medical Costs of Epidermal Growth Factor Receptor (EGFR) Mutations in Patients with Advanced EGFR Mutation-Positive Non-Small Cell Lung Cancer Treated with Afatinib in Real-World Clinical Settings in Greece

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**Purpose:** Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the preferred first-line option for patients with advanced, EGFR-mutant non-small cell lung cancer (NSCLC). Afatinib, a second-generation irreversible EGFR-TKI, has been extensively used in Greece in this setting; however, real-world data regarding molecular epidemiology and financial implications of afatinib use are lacking.

**Materials and Methods:** This was an observational, non-interventional, multicenter, retrospective cohort study, based on real-world data collected from the medical charts/records of patients treated with afatinib between 15/03/2015 and 25/06/2020 and were recorded on a web-based data capture system. Cox models were used to assess the prognostic significance of clinicopathological parameters with respect to clinical outcomes of interest. Cost analysis was conducted from a public third-payer perspective, and only direct medical costs reimbursed by the payer were considered.

**Results:** A total of 59 patients were treated with afatinib for their EGFR mutation-positive advanced NSCLC; the median age was 61 years (range: 37–91). Performance status was zero in 61%, and brain metastases were present in 13.6%. Forty-four patients (74.6%) had a deletion in exon 19 only, while nine (15.3%) had a mutation in exon 21, 8 of them in L858R and one in L861Q. At a median follow-up of 41.8 months (95% CI 35.9–51.4), the median PFS was 14.3 months (95% CI 12.2–16.4), and the median OS was 29 months (95% CI 25.6–33.4). Corresponding values for patients with deletion 19 only were 14.3 months (95% CI 11.5–18.5) and 28.1 months (95% CI 21.1–32.6), respectively. The mean expenditure for the treatment of each patient equals €25,333.68; with €21,865.06 being attributed to drug acquisition costs, €3325.35 to monitoring costs and €143.27 to adverse event treatment-related costs.

**Conclusion:** Long-term data in the real-world setting in Greece confirm activity, tolerability and cost-effectiveness of afatinib as first-line treatment of patients with advanced EGFR-mutant NSCLC.

**Clinical Trial Registration:** Clinicaltrials.gov NCT04640870.

**Keywords:** lung cancer, epidermal growth factor receptor, EGFR, afatinib, molecular epidemiology, cost-effectiveness

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## Introduction

In 2018, tracheal, bronchus and lung cancer was the leading cause of cancer-related deaths worldwide and in particular in Greece, a country that ranked fourth among 185 countries regarding the age-standardized incidence rate of lung cancer (40.5 per 100,000).<sup>1,2</sup> Non-small cell lung cancer (NSCLC) is diagnosed in approximately 80–85% of lung cancer cases, with patients often carrying driver mutations in the gene encoding for epidermal growth factor receptor (EGFR).<sup>1</sup> Advancements in the identification of molecular carcinogenesis have established EGFR tyrosine kinase inhibitors (TKIs) as the standard first-line therapy for NSCLC patients with activating EGFR mutations.<sup>3</sup> Administration of EGFR-TKI therapy has been associated with both improved outcomes and a better quality of life compared with doublet chemotherapy, as shown in several randomized Phase III clinical trials.<sup>3–8</sup>

No general consensus for a choice among any of the currently available first- and second-generation EGFR-TKIs in the first-line setting currently exists.<sup>3</sup> The only available data come from the randomized phase IIB LUX-Lung 7 trial, which showed similar objective response rates (ORR) and overall survival (OS),<sup>9,10</sup> and a modest difference in progression-free survival (PFS) for the second-generation EGFR-TKI afatinib compared to the first-generation gefitinib, and the randomized phase III ARCHER 1050 trial, where the second-generation inhibitor dacomitinib was proven to be more efficacious than the first-generation EGFR-TKI, gefitinib.<sup>11,12</sup> Nevertheless, the diverse safety profiles of first- and second-generation EGFR-TKIs contribute to the complexity of treatment decision-making in routine clinical practice.

Importantly, approximately 20% to 30% of EGFR-mutated NSCLC patients experience primary resistance to EGFR-TKIs, commonly attributed to specific genetic events, such as exon 20 insertions and the de novo T790M point mutation in the same exon.<sup>3,4</sup> Inevitably, even among patients with an initial response, the vast majority eventually progress after approximately 9 to 14 months of treatment with an EGFR-TKI.<sup>9–12</sup> Several mechanisms have been implicated in the development of acquired resistance to EGFR-TKIs, with the presence of the T790M mutation considered to be the most frequent,<sup>13</sup> identified in up to 40% of patients treated with first-generation or second-generation EGFR-TKIs.<sup>14</sup> For patients with systemic progression and a T790M mutation confirmed either with tissue biopsy or circulating-tumor DNA (ctDNA) plasma testing (and tissue re-biopsy if plasma test is negative), administration of the third-generation EGFR-TKI, osimertinib, is the treatment of choice, while for patients who are not candidates for rebiopsy or for whom a T790M mutation is not detected, the current European Society for Medical Oncology guidelines recommend switching to platinum-based chemotherapy.<sup>3</sup>

The aforementioned underscore the need for real-world evidence regarding the treatment paradigms, the use of second-generation EGFR inhibitors, namely afatinib, the molecular epidemiology, frequencies of acquired resistance mechanisms and co-occurring mutations, as well as clinical outcomes in patients with advanced or metastatic EGFR-mutant NSCLC in the frontline setting. Scarce such evidence is available in routine care settings in Greece.

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## Materials and Methods

### Study Design and Setting

This was an observational, non-interventional, single-country, multicenter, retrospective cohort study, based on real-world data collection, of patients with locally advanced or metastatic EGFR mutation-positive NSCLC who had been treated with afatinib at any line. The study was carried out by hospital-based oncologists/pulmonologists specializing in lung cancer under real-world conditions of daily clinical practice. Investigators were selected through a documented and structured feasibility process which took into consideration the physicians' qualifications, previous participation and experience in other clinical studies, recruitment potential, consistency and retention capability. In addition, in order to represent variations in current real-world patterns of care, research sites were recruited from various geographic regions in Greece, taking also into consideration the regional setting and type of healthcare site/institution (public or private specialized oncology or pulmonology clinic, academic or general hospital environment).

The study mainly involved collecting primary data, obtained retrospectively from the medical charts/records of patients treated with afatinib between 15/03/2015 and 25/06/2020. Data were recorded on a web-based data capture system, which adheres to all applicable data protection regulations and requirements concerning electronic records and database validation.

The study was designed and conducted in compliance with all applicable local laws and regulations, the Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology and the ethical principles laid down in the Declaration of Helsinki. The study was approved by the Institutional Review Board of Henry Dunant Hospital (113/3-11-2020). All patients had provided written informed consent.

### Statistical Considerations

Descriptive statistics were used to summarize patient and tumor characteristics. Categorical data, including frequencies and percentages, were summarized by contingency tables, while continuously scaled measures were described by the median and range values.

The primary endpoint of the study was progression-free survival, defined as the time from treatment initiation with afatinib as a first or second-line treatment until the

first documented disease progression, death from any cause or last follow-up, whichever occurred first (PFS1). Secondary endpoints included overall survival (OS), defined as the time from treatment initiation with afatinib until death from any cause or last follow-up, second progression-free survival (PFS2), defined as the time interval from the initiation of next treatment following discontinuation of afatinib to the date of progression, death or last contact, and assessment of the safety profile of afatinib. Survival distributions were estimated using the Kaplan-Meier method. PFS1 was assessed among patients treated with first or second-line afatinib, while OS was examined in the entire cohort. Cox models were used to assess the prognostic significance of clinicopathological parameters of interest with respect to PFS1 and OS. The SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and R studio 3.5.0 were used for data manipulation and statistical analysis.

### Cost Analysis

The cost analysis was conducted from a public third-payer (National Organization for Healthcare Services Provision (EOPYY)) perspective, and only direct medical costs reimbursed by the payer were considered. In particular, only drug acquisition costs, monitoring costs and adverse event treatment-related costs were evaluated. All costs refer to the year 2021 (€).

Drug acquisition costs per 28-day treatment cycle were calculated, taking into account the average dose per cycle of the patients included in the cohort and the price reimbursed from EOPYY. As afatinib is exclusively provided by a hospital or EOPYY pharmacies, its official hospital price, minus the compulsory hospital rebate (5%) was considered the price reimbursed by the public payer, which is equal across all different strengths of afatinib.<sup>15</sup> The calculation of the hospital price was in line with the pricing methodology legislated by the Ministry of Health (MoH) and the latest Drug Price Bulletin issued by the MoH (December 2020).<sup>15-17</sup>

Monitoring costs were estimated based on the utilization of monitoring services by the cohort both prior treatment initiation and during treatment with afatinib. The unit costs per monitoring service were obtained from the national tariff of medical practices published by EOPYY.<sup>18</sup> Moreover, adverse event treatment-related costs were only considered for Grade 3-4 adverse events, with their reimbursement costs being obtained from the corresponding Diagnosis Related Group (DRG) tariffs issued by the MoH.<sup>19</sup>

## Results

### Clinicopathological Characteristics

From 15/03/2015 through 25/06/2020, a total of 59 patients were treated with afatinib for their EGFR mutation-positive advanced lung cancer. More patients were of younger age (<65 years, 59.3%), with PS 0 (61.0%) and no brain metastases (86.4%) at the time of afatinib administration. The median age was 61 years (range 37–91). Patient and tumor characteristics are displayed in Table 1.

Afatinib was administered as first-line treatment in 86.4% of the study cohort (n=51 patients), second-line treatment in five patients (8.5%) and as third-line and beyond in three patients (5.1%). Most patients initially received afatinib at a dose of 40 mg/day (53 patients; 89.8%), while in five patients (8.5%) the drug was administered at a dose of 30 mg/day in the first cycle of treatment and one patient received 4 cycles of afatinib at a dose of 20 mg/day per cycle.

**Table 1** Patient and Tumor Characteristics

	Total (N=59)
<b>Age<sup>^</sup></b>	
Median (min, max)	60.7 (37.4, 90.5)
	<b>N (%)</b>
<65	35 (59.3)
≥65	24 (40.7)
<b>Sex</b>	
Female	29 (49.2)
Male	30 (50.8)
<b>Smoking*</b>	
No	29 (50.0)
Yes	29 (50.0)
<b>Histology</b>	
Adenocarcinoma	56 (94.9)
Squamous cell	3 (5.1)
<b>PS<sup>^</sup></b>	
0	36 (61.0)
1	21 (35.6)
2	1 (1.7)
3	1 (1.7)
<b>Brain metastases<sup>^</sup></b>	
No	51 (86.4)
Yes	8 (13.6)

**Notes:** \*Data not available for all subjects. Missing values: Smoking= 1. <sup>^</sup> At afatinib administration.

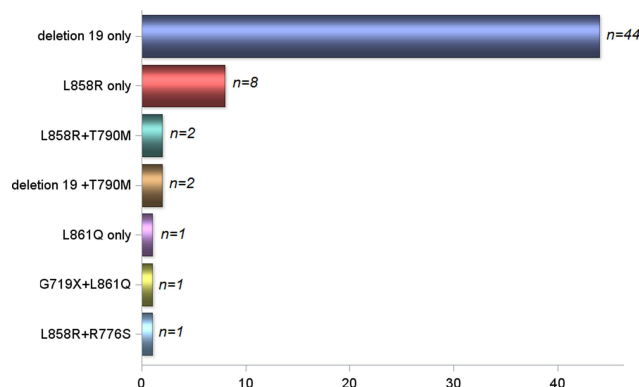
**Abbreviation:** PS, Performance status.

### Molecular Epidemiology

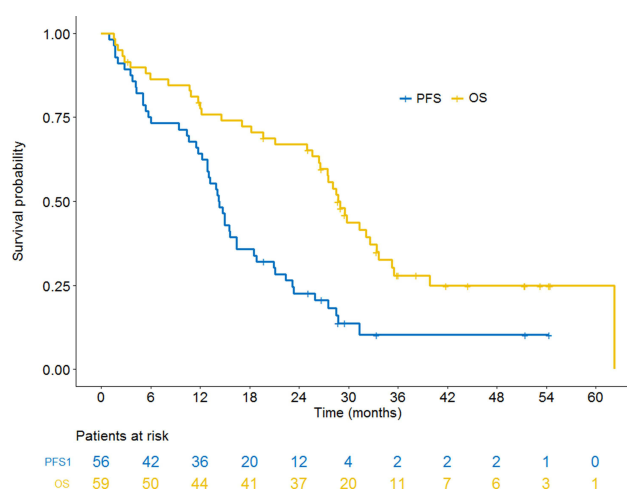
Forty-four patients (74.6%) had a deletion in exon 19 only, while nine (15.3%) had mutation in exon 21; 8 of them in L858R and one in L861Q. In addition, one patient carried EGFR co-mutations in G719X in exon 18 and in L861Q in exon 21. Two additional patients harbored a deletion in exon 19 along with a T790M mutation in exon 20, respectively. In three patients, the mutations were observed in exon 20 and 21; two of them had mutation in T790M and L858R and one in R776S and L858R, respectively (Figure 1).

### PFS1

At a median follow-up of 41.8 months (95% CI 35.9–51.4), 48 PFS1 events had been reported among patients who received afatinib as a first- or second-line treatment (85.7%) and 40 patients (67.8%) had died overall. The median PFS1 was 14.3 months (95% CI 12.2–16.4) and the median OS was 29 months (95% CI 25.6–33.4) (Figure 2). The median PFS1 and OS for patients with



**Figure 1** Type of EGFR mutation detected.



**Figure 2** Kaplan-Meier curves with respect to PFS1 and OS.

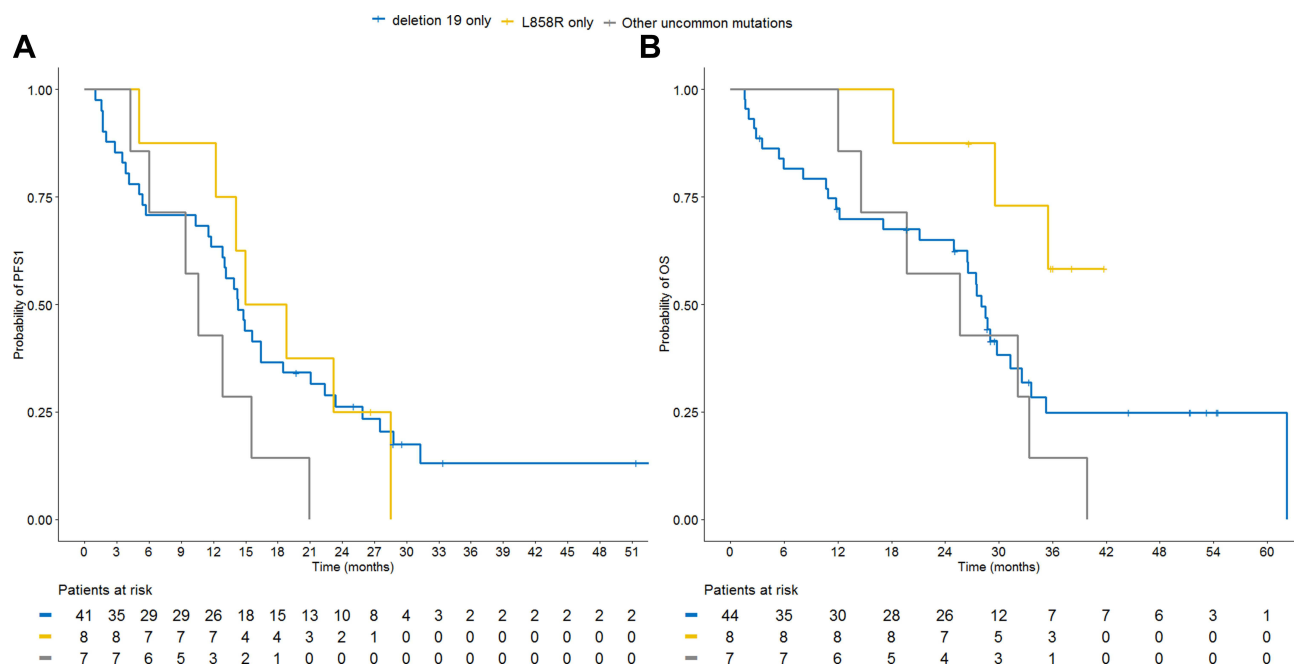
deletion 19 only was 14.3 months (95% CI 11.5–18.5) and 28.1 months (95% CI 21.1–32.6), respectively. All seven patients with uncommon mutations died of their disease. Out of eight patients with L858R mutations, seven (87.5%) had experienced a disease progression and three had died (37.5%) at the time of the analysis. The Kaplan-Meier curves with respect to PFS1 and OS by EGFR mutation type are presented in Figure 3A and B, respectively.

The patient with an L861Q EGFR mutation only was a 73-year-old male who progressed after 6 months of afatinib treatment and died 6 months later. Additionally, a 44-year-old female patient carrying EGFR mutation in G719X and L861Q progressed within 4 months upon administration of afatinib and died 10 months after progressive disease documentation. Both patients with a deletion 19 and a T790M mutation progressed in 12.9- and 9.4-months post afatinib initiation, respectively. Of them, the first patient died 19.7 months and the other one 9.4 months since treatment initiation. Performance status was the only parameter that showed prognostic significance for OS with patients with PS 1–3 being at higher risk for death as compared to those with PS 0 (HR=2.23, 95% CI 1.17–4.24, Wald’s p=0.015), while no significance was reached in terms of PFS1 (p=0.96). The rest of the examined clinicopathological parameters were not found to be prognostic for either PFS1 or OS (data not shown).

At the cut-off date for the analysis (November 2020), 7 patients (11.9%) were still on active treatment with afatinib. All of them had deletion in exon 19 only. The median time to treatment discontinuation was 14.1 months (95% CI 10.3–16.4).

### Post-Afatinib Treatment and PFS2

Out of the 46 patients with a documented disease progression after afatinib administration, 37 (80.4%) received other treatments including immunotherapy alone (n=3; 8.1%), TKIs only (n=18; 48.6%), TKI with immunotherapy (n=1; 2.7%), combination chemotherapy (n=3; 8.1%), chemotherapy alone (n=2; 5.4%), chemotherapy combined with immunotherapy (n=6; 16.2%), and chemotherapy in combination with immunotherapy and anti-VEGF (n=4; 10.8%). Of note, one patient with R776S+L858R EGFR mutation received afatinib beyond disease progression. Details of subsequent treatment after failure of afatinib therapy per patient are presented in [Supplementary Table 1](#). Thirty-five of them (94.6%) had received afatinib as a first-line treatment, while the drug was administered as a second-line therapy in the remaining two patients. Upon failure of afatinib as a second-line therapy, one patient carrying a deletion 19 and T790M EGFR mutation was treated with osimertinib and one with a G719X and L861Q EGFR mutation received pemetrexed and carboplatin. The median time to the next treatment was 17 days upon the last



**Figure 3** Kaplan-Meier curves based on the type of EGFR mutation with respect to (A) PFS1 and (B) OS.



cycle of afatinib. Thirty-three of the 37 patients (89.2%) experienced a second progression and the median PFS2 was 6.3 months (95% CI 3.0–9.3).

## Adverse Events

Overall, 42 patients (71.2%) experienced at least one adverse event during afatinib treatment and 7 (11.9%) had grade 3 or 4 events. The incidence of all adverse events during afatinib treatment is depicted in Table 2. Two grade 4 events of rash and clinic infection were reported in one patient who discontinued afatinib due to soft tissue infection. Three additional patients discontinued treatment with afatinib due to non-fatal toxicity, while no fatal adverse events were reported throughout treatment. The most commonly reported adverse events were diarrhea (29 patients; 49.2%)

followed by rash (24 patients; 40.7%) and were mostly of grade 1 or 2.

## Cost Analysis

Drug acquisition costs per 28-day cycle of treatment are equal to €1385.15 regardless of the afatinib strength administered to the cohort (Table 3).

In addition, costs associated with monitoring services utilized prior treatment initiation equal €453.16, while after initiation of afatinib monitoring costs equal €181.95 per 28-day cycle (Table 4).

Lastly, adverse event treatment-related cost per patient was estimated to equal €143.27 per 28-day cycle (Table 5).

Moreover, taking into consideration that each member of the cohort remained on treatment with afatinib for an

**Table 2** Incidence of Grade 1–4 Toxicities Throughout Afatinib Treatment

Adverse event	Grade 1		Grade 2		Grade 3		Grade 4	
	N of pts	% pts	N of pts	% pts	N of pts	% pts	N of pts	% pts
<b>Overall</b>	29	49.15	28	47.46	7	11.86	1	1.69
Acne	0	0.00	3	5.08	0	0.00	0	0.00
Creatinine	1	1.69	0	0.00	0	0.00	0	0.00
Cough	1	1.69	0	0.00	0	0.00	0	0.00
Dermatitis	1	1.69	1	1.69	0	0.00	0	0.00
Diarrhea	6	10.17	21	35.59	2	3.39	0	0.00
Dry skin	0	0.00	1	1.69	0	0.00	0	0.00
Fatigue	2	3.39	3	5.08	0	0.00	0	0.00
Fever	0	0.00	0	0.00	1	1.69	0	0.00
Hemoglobin	5	8.47	0	0.00	0	0.00	0	0.00
Infection clinic	0	0.00	0	0.00	0	0.00	1	1.69
Leucocytes	1	1.69	0	0.00	0	0.00	0	0.00
Mucositis clinical	4	6.78	1	1.69	0	0.00	0	0.00
Mucositis functional	3	5.08	1	1.69	0	0.00	0	0.00
Nail changes	1	1.69	1	1.69	0	0.00	0	0.00
Nausea	2	3.39	1	1.69	0	0.00	0	0.00
Neuropathy sensory	1	1.69	0	0.00	0	0.00	0	0.00
Neutrophils	1	1.69	0	0.00	0	0.00	0	0.00
Nose bleeding	2	3.39	1	1.69	0	0.00	0	0.00
Paronychia	2	3.39	0	0.00	0	0.00	0	0.00
Pain bone	2	3.39	2	3.39	0	0.00	0	0.00
Pain muscle	2	3.39	0	0.00	0	0.00	0	0.00
Pneumonitis	2	3.39	0	0.00	0	0.00	0	0.00
Pruritus	3	5.08	0	0.00	0	0.00	0	0.00
Pulmonary embolism	0	0.00	0	0.00	1	1.69	0	0.00
Rash	16	27.12	4	6.78	3	5.08	1	1.69
Stomatitis	1	1.69	0	0.00	0	0.00	0	0.00
Vomiting	0	0.00	1	1.69	0	0.00	0	0.00
Weakness	1	1.69	0	0.00	0	0.00	0	0.00

**Abbreviations:** N, number; pts, patients.

**Table 3** Drug Acquisition Costs

Pharmaceutical Intervention	Proportion of Treatment Cycles the Intervention was Administered	Number of Packs Administered per 28-Days Cycle	Drug acquisition cost per pack	Drug Acquisition Cost per 28-Days Cycle
Afatinib 40mg/TAB BTx28	76.3%	1.00	€ 1385.15	€ 1385.15
Afatinib 30mg/TAB BTx28	11.0%	1.00	€ 1385.15	€ 1385.15
Afatinib 20mg/TAB BTx28	12.7%	1.00	€ 1385.15	€ 1385.15
<b>Total drug acquisition cost per 28-days cycle per patient treated with afatinib</b>				<b>€ 1385.15</b>

**Table 4** Monitoring Costs

<b>One-Off Monitoring Costs Prior Treatment Initiation with Afatinib</b>			
Type of Monitoring Service	Units of Monitoring Services Utilized Prior Treatment Initiation with Afatinib	Cost per Unit of Monitoring Service	Total Monitoring Services Utilization Costs Prior Treatment Initiation with Afatinib
Full Blood Count	1.00	€ 2.88	€ 2.88
Computed tomography (CT) of the chest	1.00	€ 71.11	€ 71.11
Computed tomography (CT) of the upper abdomen	1.00	€ 71.11	€ 71.11
Computed tomography (CT) of the lower abdomen	1.00	€ 71.11	€ 71.11
Magnetic resonance imaging (MRI) of the brain	1.00	€ 236.95	€ 236.95
<b>Total one-off monitoring cost prior treatment initiation with afatinib per patient</b>			<b>€ 453.16</b>
<b>Monitoring cost while on treatment with afatinib</b>			
Type of monitoring service	Units of monitoring services utilized per 28-days treatment cycle	Cost per unit of monitoring service	Total monitoring services utilization costs per 28-days treatment cycle
Outpatient visit	0.92	€ 10.00	€ 9.21
Full Blood Count	0.92	€ 2.88	€ 2.65
Computed tomography (CT) of the chest	0.31	€ 71.11	€ 21.82
Computed tomography (CT) of the upper abdomen	0.31	€ 71.11	€ 21.82
Computed tomography (CT) of the lower abdomen	0.31	€ 71.11	€ 21.82
Magnetic resonance imaging (MRI) of the brain	0.31	€ 236.95	€ 72.71
Chest X-ray	0.31	€ 4.05	€ 1.24
PET/CT scan	0.08	€ 400.00	€ 30.68
<b>Total monitoring cost while on treatment with afatinib per 28-days cycle per patient</b>			<b>€ 181.95</b>

average of 15.79 treatment cycles, the mean expenditure for EOPYY for the treatment of each patient with afatinib equals €25,333.68; with €21,865.06 being attributed to drug acquisition costs, €3325.35 to monitoring costs and €143.27 to adverse event treatment-related costs (Table 6).

## Discussion

The current study was the first attempt to record the molecular epidemiology of patients treated with afatinib

for advanced, EGFR-mutated NSCLC in Greece. We found that real-life clinical practice treatment patterns reflected the outcomes of larger randomized trials that led to its approval. Afatinib was mainly used as first-line treatment, based on its superior efficacy as compared to the first-generation inhibitors and its presumed activity in rare mutations.<sup>14,20</sup> The majority of patients harbored deletion 19 mutation, which reflects the reported higher efficacy of afatinib in this specific mutation type.<sup>21,22</sup> Tumors

**Table 5** Adverse Event Treatment-Related Costs

Adverse event	Incidence of Grade 3–4 Adverse Event per Patient	Cost per Adverse-Event (DRG Cost)	DRG Code
Rash	0.068	€ 708.00	D27M
Diarrhea	0.034	€ 1033.00	P55M
Fever	0.017	€ 428.00	P23A
Pulmonary embolism	0.017	€ 1365.00	K35M
Infection clinic*	0.017	€ 1762.00	A22Ma
<b>Total adverse event treatment-related cost per patient treated with afatinib</b>		<b>€ 143.27</b>	-

**Note:** \*DRG cost of pneumonia employed, as no specific cost for infection clinic is currently available within the DRG tariff.

**Table 6** Mean Expenditure for EOPYY per Patient Treated with Afatinib

Cost Component	EOPYY Expenditure per Patient Treated with Afatinib*
Drug acquisition costs	€ 21,865.06
Monitoring costs	€ 3325.35
Adverse event treatment-related costs	€ 143.27
<b>Total EOPYY expenditure per patient treated with afatinib</b>	<b>€ 25,333.68</b>

**Note:** \*Costs were calculated taking into consideration that each patient remained on afatinib treatment for an average of 15.79 treatment cycles.

with exon 19 deletion are known to carry a better prognosis, as compared to other mutations and especially the L858R point mutation in exon 21.<sup>14,20–22</sup> Regarding afatinib, combined analysis of the LUX-LUNG 3 and LUX-LUNG 6 phase III trials has shown that in the subgroup of patients whose tumors harbored an exon 19 deletion, treatment with afatinib was associated not only with a PFS benefit, but also with a substantial and clinically significant survival benefit, as compared to first-generation inhibitors.<sup>6,7</sup> This notion is presumed to have affected the clinical practice patterns of oncologists and pneumonologists in Greece who were more likely to prescribe afatinib for patients with exon 19 deletion.

Another important aspect of afatinib administration is its use in the uncommon EGFR mutations, based on preclinical data suggesting that it is active against a broad spectrum of uncommon mutations, especially in eons 18 and 29, due to its unique action as a pan-EGFR inhibitor.<sup>23–26</sup> These properties lead to its approval by FDA for the treatment of patients with uncommon mutations, where it exerts higher activity than erlotinib or gefitinib, albeit some uncommon mutations are notoriously refractive to treatment, even with

afatinib and carry a poor prognosis.<sup>24,26,27</sup> These results were confirmed in our cohort, where patients with uncommon mutations or with co-existence of a common and uncommon mutation had poorer clinical outcomes with afatinib treatment, as compared to the Deletion 19 subgroup. A special reference should be made to the T790M resistance mutation, which is notoriously refractory to all first-generation inhibitors, including erlotinib and gefitinib, and is held responsible for primary resistance to these drugs, at least in a subset of patients.<sup>27,28</sup> Afatinib has been shown to be active against the T790M mutation in vitro, but this activity has not been consistently translated into substantial clinical benefit in clinical trials.<sup>26,28</sup> This observation was consistent with our findings, with mixed responses to afatinib in patients with tumors harboring the T790M mutation, ranging from 9 to 17 months, in terms of overall survival. The advent of the third-generation EGFR-TKI osimertinib with a documented activity against T790M has completed transformed the landscape of the treatment of EGFR-mutant NSCLC, and currently osimertinib dominates the first-line treatment in this setting, due to its high activity and favorable toxicity.<sup>29,30</sup> Nevertheless, it should be noted that osimertinib was not available in Greece for the largest period during the accrual period of the study. Notably, a sequential strategy with afatinib as first-line treatment, followed by osimertinib at the time of development of the exon 20 T790M-resistance mutation has been shown to be both feasible and efficient in real-world clinical settings.<sup>33</sup> This concept is further facilitated by the use of liquid biopsy to identify the T790M mutation in the blood with digital droplet PCR.<sup>34</sup>

Afatinib is considered to be more toxic than first-generation inhibitors, especially in terms of diarrhea, due to its mechanism of action, which blocks the action of all proteins of the HER family of receptors and not just EGFR.<sup>25–27</sup> In our cohort, we confirmed that acmoid rash



and diarrhea are the two main concerns with afatinib safety profile, but, similar to the clinical trials, in the vast majority of cases adverse events were manageable and did not lead to discontinuation of the drug.

Finally, the cost analysis conducted demonstrated that the mean cost associated with afatinib treatment reimbursed from EOPYY equaled €25,333.68 per patient, with costs related to drug acquisition forming the primary cost driver. The findings of the analysis conducted are consistent with two other published economic evaluation studies conducted in France and China.<sup>31,32</sup> Both studies assessed the cost-effectiveness of afatinib versus comparator treatments and concluded that the major cost component associated with afatinib treatment is drug acquisition costs followed by the monitoring and the adverse event treatment-related costs.<sup>31,32</sup>

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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