Original Study

Management of Italian Patients With Advanced Non–Small-Cell Lung Cancer After Second-Line Treatment: Results of the Longitudinal Phase of the LIFE Observational Study

Filippo de Marinis,[1,2] Andrea Ardizzoni,[3] Gabriella Fontanini,[4] Francesco Grossi,[5] Federico Cappuzzo,[6] Silvia Novello,[7] Antonio Santo,[8] Vito Lorusso,[9] Diego Cortinovis,[10] Monica Iurlaro,[11] Domenico Galetta,[12] Cesare Gridelli[13], on behalf of the LIFE study team

Abstract

After second-line therapy, patients with advanced non–small-cell lung cancer (NSCLC) might receive further treatment. The primary aim of the longitudinal phase of the LIFE (non–small-cell Lung cancer management In patients progressing after First linE of treatment in the metastatic setting) study was to describe the portion of patients who, after second-line treatment according to clinical practice, received third-line therapy outside of a clinical trial. This portion was not negligible: third-line chemotherapy or erlotinib was administered to 158 patients (40.4%).

Introduction/Background: Patients with advanced NSCLC who experience disease progression after second-line therapy might receive further active treatment. LIFE was an Italian cohort multicenter observational study composed of a cross-sectional and a longitudinal phase. **Patients and Methods:** In the longitudinal phase, described here, the primary aim was to determine the proportion of patients receiving third-line therapy among those who received second-line active treatment according to clinical practice. The proportion of patients receiving further treatment lines was also estimated. **Results:** The longitudinal phase was conducted between January and August 2012. Of 464 patients who began second-line therapy outside of clinical trials within the baseline evaluation, 56 (12.1%) were still receiving second-line therapy at the end of the observation period and 17 (3.7%) withdrew during or after second-line therapy. Of the remaining 391 patients, 158 (40.4%) received third-line treatment outside of clinical trials: 93 received a third-line chemotherapy and 65 a targeted agent. The main reason for interrupting third-line treatment was disease progression or death. During the same observation period, 25 of 113 patients who completed a third-line therapy received a fourth line of treatment. From diagnosis of NSCLC to the end of observation, biomarkers were tested in 323 patients (59.7%): epidermal growth factor receptor mutations in 315 (58.2%), Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) mutations in 83 (15.3%) and Anaplastic lymphoma kinase (ALK) translocation in 84 (15.5%). **Conclusion:** In Italian clinical practice, the proportion of patients with advanced NSCLC receiving more than 2 treatment lines of therapy is not negligible.

Clinical Lung Cancer, Vol. 15, No. 5, 338-45
Keywords: Chemotherapy, EGFR, Erlotinib, NSCLC, Third-line

The members of the LIFE study team are enlisted in Appendix 1.

[1]UOC Pneumologia Oncologica, A.O. San Camillo Forlanini, Rome, Italy
[2]Thoracic Oncology Division, European Institute of Oncology (IEO), Milan, Italy
[3]U.O. Oncologia Medica, Azienda Ospedaliera di Parma, Parma, Italy
[4]U.O. Oncologia II Univ., Azienda Ospedaliero Universitaria Pisana, Pisa, Italy
[5]S.S. Tumori Polmonari, IRCCS A.O.U. San Martino-IST Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy
[6]Oncologia, Ospedale di Livorno – Oncologia, Livorno, Italy
[7]Oncologia, Università di Torino; A.O.U. San Luigi Gonzaga, Orbassano, Italy
[8]GIVOP (Gruppo Interdisciplinare Veronese Oncologia Polmonare), Ospedale Civile Maggiore Borgo Trento - Oncologia Medica D.O., Verona, Italy
[9]Oncologia Medica Pad. oncologico Ospedale V. Fazzi, Lecce, Italy
[10]UO Oncologia Medica Ospedale San Gerardo, Monza, Italy
[11]Boehringer Ingelheim S.p.A., Milano, Italy
[12]Oncologia Medica IRCCS Giovanni Paolo II Ospedale Oncologico, Bari, Italy
[13]Oncologia Medica, A.O.R.N. San Giuseppe Moscati, Avellino, Italy

Submitted: Jan 17, 2014; Revised: Apr 7, 2014; Accepted: Apr 8, 2014; Epub: May 14, 2014

Address for correspondence: Filippo de Marinis, MD, European Institute of Oncology (IEO), Via Ripamonti 435, 20141 Milan, Italy
E-mail contact: filippo.demarinis@ieo.it

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.clc.2014.04.004

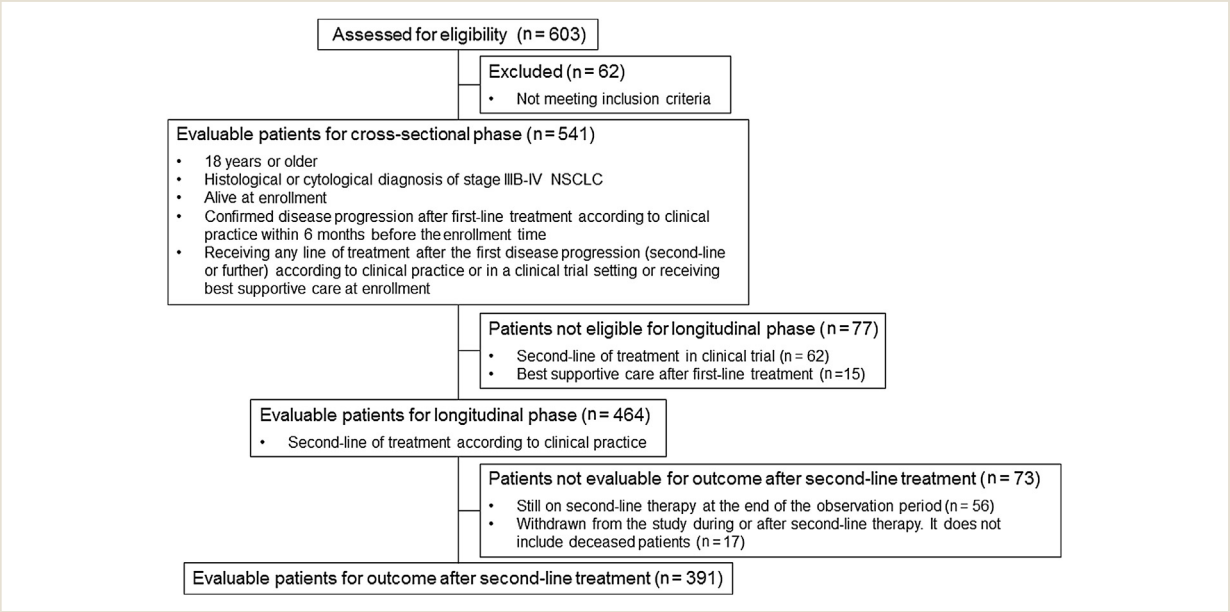
Introduction

Patients in whom first-line treatment for advanced non–small-cell lung cancer (NSCLC) has failed have a limited life expectancy.[1] However, these patients might be candidates to receive further treatment, with the aim of prolonging survival, but also of obtaining palliation of symptoms and benefit in health-related quality of life. Based on evidence from randomized trials, current international guidelines consider either chemotherapy or epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors as options for further treatment after failure of first-line therapy.[2-5] Docetaxel[6,7] and pemetrexed[8,9] are the cytotoxic drugs approved for use as second-line treatment. Erlotinib, an orally administered EGFR tyrosine kinase inhibitor, was approved for second- or third-line treatment after demonstrating a significant prolongation of overall survival and benefit in quality of life compared with placebo in patients not selected for histology or EGFR mutation status in whom 1 or 2 lines of chemotherapy had failed.[10] In 2010, gefitinib was approved by the European Medicines Agency for any line of treatment in patients with tumors carrying activating EGFR mutations, which are present in 10% to 15% of Western patients.[11] The association between the presence of EGFR mutations and the efficacy of EGFR tyrosine kinase inhibitors was the first strong interaction between a molecular predictive factor and the efficacy of drugs in advanced NSCLC.[12-18] More recently, crizotinib demonstrated high efficacy in patients selected for the presence of Anaplastic lymphoma kinase (ALK) translocations.[19] Since 2013, crizotinib has been available in Italy for the second-line treatment of these patients, but before 2013 it was available only in the context of clinical trials.

The prognosis for patients receiving second-line treatment can be very heterogeneous.[1,20] Some patients with negative prognostic factors have a very bad prognosis, challenging the opportunity for further active treatment. On the contrary, other patients have a better life expectancy, and many oncologists consider the opportunity for further active treatment after the failure of second-line therapy. Erlotinib is the only drug with evidence of efficacy as third-line treatment, and this evidence is lacking for cytotoxic drugs.

The observational LIFE (non–small-cell Lung cancer management In patients progressing after First linE of treatment in the metastatic setting) study was conducted with the aim of describing the management of patients with advanced NSCLC in clinical practice, after first-line treatment failure. The cross-sectional phase of the LIFE study, reported elsewhere,[21] documented the administration of second-line treatment (chemotherapy or targeted agents), according to routine clinical practice, in a relevant proportion of patients enrolled in the study. In fact, among enrolled patients alive after first-line disease progression, 86% received a second line treatment according to clinical practice, 11% clinical trial, and 3% best supportive care (BSC). In the present report, data from the longitudinal phase of the study are reported. The primary aim of this longitudinal, follow-up phase was to describe outcome of patients after second-line treatment in terms of the proportion of patients who received a third line of treatment according to routine clinical practice (outside of clinical trials), among the cohort of patients who had received second-line active treatment according to clinical practice. The proportion of patients receiving further lines of treatment was also evaluated. Secondary end points included the execution and characteristics of molecular analyses (EGFR, Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) mutation, and ALK translocation) performed from NSCLC diagnosis to the end of observation. The proportion of cases tested for biomarkers has greatly increased in recent years, after the improved knowledge of tumor biology and the identification of molecular predictive factors for the

Figure 1 Patient Flow Chart



Abbreviation: NSCLC = Non–Small-Cell Lung Cancer.

efficacy of several drugs, like EGFR tyrosine kinase inhibitors for EGFR-mutated cases and crizotinib for cases with ALK translocation. The availability of these drugs is expected to substantially increase the number of advanced NSCLC patients undergoing molecular testing.

Patients and Methods

Study Design and Entry Criteria

LIFE was a cohort multicenter observational study, involving 60 oncology and pneumology centers in Italy. The study, as detailed elsewhere,[21] included a cross-sectional phase, followed by a longitudinal, follow-up phase. The cross-sectional data were collected during the inclusion visit and referred to the previous 6 months, and the subsequent longitudinal evaluation was based on a 6-month follow-up period. The criteria for patient eligibility for the cross-sectional and the longitudinal phase of the study are shown in Figure 1. Only patients with advanced stage IIIB to IV NSCLC (the VII edition of tumor, node, metastases classification was available during the enrollment period) who had started active second- or further line therapy according to routine clinical practice at the cross-sectional evaluation were eligible for the longitudinal phase of the study. The analyses of treatment lines reported herein included all patients who received therapy during the follow-up period or before the baseline visit. Instead, results of biomarker analyses were included from NSCLC diagnosis to the end of observation, thus including all evaluable patients at the enrollment visit (n = 541).

The LIFE protocol was approved by the independent ethical committees of each participating institution.

Data Collection and Methods

The information requested was collected using an electronic data capture system. Results from cross-sectional evaluation are described elsewhere.[21] Patients underwent clinical examination at enrollment and then were followed up for 6 months.

Third-line treatment was defined by the clinician as any chemotherapy or targeted therapy administered in this setting according to routine clinical practice or in a clinical trial. Patients were considered as receiving BSC alone when they did not start any further line of active treatment as defined herein. Further lines of treatment were defined similarly.

Aims of the Study, Sample Size, and Statistical Analysis

The primary aim of the longitudinal phase was to describe the proportion of patients who received third-line treatment according to routine clinical practice, among those who received second line active treatment according to routine clinical practice. Secondary end points were to describe the proportion of patients in whom EGFR and KRAS mutation analysis were performed and those who received ALK translocation testing from the time of NSCLC diagnosis. Also, secondary end points included the description of biomarker analyses timing, mutation details, and characteristics of patients who were part of the analysis.

The sample size of the LIFE study was calculated considering available data from local center databases confirmed by Steering Committee members of the study on the proportion of patients who received second- and third-line treatment, as described elsewhere.[21] Five hundred patients were planned to be enrolled. Larger sample size meant greater estimate precision.

Mean, standard deviation (SD), median, and interquartile range (IQR) values were used to describe the distribution of quantitative variables and absolute and relative frequencies for categorical values. Missing data were not imputed.

Statistical analyses were performed using SAS for Windows, release 9.2 (SAS Institute Inc).

Results

Patient Characteristics

Of 603 patients referred to 60 Italian oncology and pneumology centers during the recruitment period (between July 2011 and January 2012) and consecutively enrolled in the study, 541 (89.7%) met the inclusion criteria of the cross-sectional phase. Median number of patients enrolled at each Institution was 7 (range, 1-41). Of these 541 patients, 15 received only BSC after first-line treatment, 62 were included in second-line treatment clinical trials, the remaining 464 (85.8%) received a second-line treatment according to routine clinical practice and were evaluated for the longitudinal phase of the study, performed between January and August 2012 (Fig. 1). Table 1 shows the main characteristics of the 464 evaluated patients. Most patients were male (n = 326, 70.3%), with a median

Table 1 Baseline Characteristics of Patients With Second-Line Treatment in Clinical Practice (n = 464)

Parameter	Patients, n (%)
Baseline Characteristics	
Gender	
Male	326 (70.3)
Female	138 (29.7)
Stage of Disease at Diagnosis	
IIIB	123 (26.5)
IV	341 (73.5)
Histotype	
Adenocarcinoma	333 (71.8)
Squamous	81 (17.5)
Large cell	9 (1.9)
Not otherwise specified	19 (4.1)
Other	22 (4.7)
Characteristics at Second-Line Treatment Start	
Age at the second line treatment start	
Median	66
Range	30-84
ECOG Performance Status	
0	143 (30.8)
1	233 (50.2)
2	65 (14.0)
3	3 (0.7)
Not available	20 (4.3)
Smoking status	
Current	99 (21.3)
Former	207 (44.6)
Never	110 (23.7)
Not available	48 (10.3)

age of 66 years at the start of second-line treatment (range, 30-84 years). A total of 341 patients (73.5%) had stage IV disease, and adenocarcinoma was the histologic type in 333 patients (71.8% of cases). Performance status (PS) was 0 or 1 in 376 patients (81.0%). Patients were never smokers in 23.7% of cases (n = 110).

First- and Second-Line Therapy

Details about first-line chemotherapy are reported elsewhere.[21] Briefly, first-line chemotherapy (mostly combination) treatment, with or without targeted therapy, was administered to 506 patients (93.5%) for locally-advanced or metastatic NSCLC. Among patients treated with chemotherapy, the most frequently used regimens were platinum-pemetrexed (n = 223, 44.1%), and platinum-gemcitabine (n = 156, 30.8%). Bevacizumab was administered in combination with chemotherapy, mainly with carboplatin-paclitaxel or cisplatin-gemcitabine, in 21 (3.9%) patients. Gefitinib, approved for the treatment of EGFR mutated patients, was administered to 32 (5.9%) patients, and erlotinib to 5 (0.9%) patients.

Among 464 patients evaluated in this longitudinal analysis, chemotherapy was used as second-line treatment in 301 (64.9%) patients, mostly as a single agent. Chemotherapy with bevacizumab was administered in 3 patients and another targeted agent, such as EGFR tyrosine kinase and ALK inhibitors, in 160 patients (34.5%) (Table 2). Palliative radiotherapy was administered in combination with systemic therapy in 53 patients (11.4%).

Table 2 Summary of Second-Line Therapies Outside of Clinical Trials (n = 464)

Therapy	Patients, n (%)
Single-Agent Chemotherapy (n = 241; 51.9%)	
Docetaxel	118 (25.4)
Pemetrexed	68 (14.7)
Gemcitabine	26 (5.6)
Vinorelbine	23 (5.0)
Carboplatin	2 (0.4)
Cisplatin	2 (0.4)
Paclitaxel	2 (0.4)
Combination Regimen (n = 63; 13.6%)	
Carboplatin/Gemcitabine	15 (3.2)
Cisplatin/Pemetrexed	14 (3.0)
Docetaxel/Gemcitabine	9 (1.9)
Carboplatin/Paclitaxel	8 (1.7)
Carboplatin/Pemetrexed	7 (1.5)
Cisplatin/Gemcitabine	5 (1.1)
Cisplatin/Vinorelbine	1 (0.2)
Cisplatin/Paclitaxel	1 (0.2)
Carboplatin/Etoposide	1 (0.2)
Docetaxel/Vinorelbine	1 (0.2)
Carboplatin/Vinorelbine	1 (0.2)
Targeted Therapies (n = 163; 35.1%)	
Erlotinib	149 (32.1)
Gefitinib	9 (1.9)
Bevacizumab (added to CBDCA and PAC)	3 (0.6)
Crizotinib	2 (0.4)

Abbreviations: CBDCA = carboplatin; PAC = paclitaxel.

Outcome of Patients After Second-Line Treatment: Third-Line Treatment

Out of 464 patients who had started active second-line therapy outside of clinical trials, 56 patients (12.1%) were still receiving second-line treatment at the end of the 6-month observation period and 17 (3.7%) withdrew from the study during or after second-line treatment (Fig. 1). Of the remaining 391, 158 patients (40.4%) received third-line systemic treatment outside of clinical trials, during the observation period (Fig. 2). Details of third-line treatments are reported in Table 3. In summary, 93 patients received third-line chemotherapy (single-agent in most cases: vinorelbine, docetaxel, and gemcitabine were the 3 most frequently used agents) and 65 patients received a targeted agent (erlotinib in 64 cases).

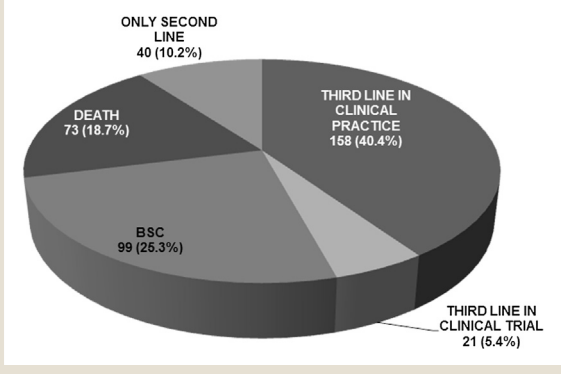
Of 158 patients who received a second- and a third-line treatment during the observation period, 53 patients (33.5%) received chemotherapy (with or without bevacizumab) in both lines, and the remaining 105 received a targeted agent (mostly erlotinib) as second- or third-line therapy.

The median number of treatment cycles of third-line treatment was 3 (IQR, 2-4; range, 1-11) with single-agent chemotherapy, 3 cycles (IQR, 2-4; range, 1-8) with combination chemotherapy, and the treatment duration was 2.4 months (IQR, 1.5-3.8; range, 0-6.9) with erlotinib. However, some patients were still receiving treatment at the end of the observation period.

Partial responses were observed in 3 patients (1.9%), stable disease was observed in 16 (10.1%), and disease progression in 70 (44.3%); 69 patients had no available data.

The main reason for interruption of third-line treatment (chemotherapy and erlotinib) was disease progression or death, and the proportion of patients who stopped treatment because of toxicity was small (8 of 58 with chemotherapy and 4 of 44 with erlotinib). During the same observation period, 25 of 113 patients who completed a third-line treatment received a fourth-line treatment, and 2 of these patients also received a fifth-line treatment.

Figure 2 Outcome of Patients After Second-Line Treatment (n = 391)



Abbreviation: BSC = Best Supportive Care.

Table 3 Summary of Third-Line Therapies Outside of Clinical Trials (n = 158)

Therapy	Patients, n (%)
Single-Agent Chemotherapy (n = 83; 52.5%)	
Vinorelbine	32 (20.3)
Docetaxel	25 (15.8)
Gemcitabine	16 (10.1)
Pemetrexed	6 (3.8)
Paclitaxel	3 (1.9)
Topotecan	1 (0.6)
Combination Regimens (n = 10; 6.3%)	
Gemcitabine/Vinorelbine	3 (1.9)
Carboplatin/Gemcitabine	2 (1.3)
Carboplatin/Pemetrexed	1 (0.6)
Carboplatin/Vinorelbine	1 (0.6)
Docetaxel/Gemcitabine	1 (0.6)
Docetaxel/Vinorelbine	1 (0.6)
Cisplatin/Gemcitabine	1 (0.6)
Targeted Therapies (n = 65; 41.1%)	
Erlotinib	64 (40.5)
Other (not specified)	1 (0.6)

Biomarker Analysis

This report describes biomarker analyses performed for all evaluable patients at the enrollment visit (n = 541) in the period of time between diagnosis of NSCLC and the end of observation.

Of 541 patients eligible for the cross-sectional phase of the study, biomarker analysis (EGFR mutation and/or KRAS mutation and/or ALK translocation) was performed in 323 patients (59.7%). EGFR mutation was tested in 315 (58.2%), KRAS mutation in 83 (15.3%), and ALK translocation in 84 (15.5%) patients. Characteristics of patients tested for biomarkers, compared with those without biomarker analysis, are reported in Table 4. The age of patients tested for biomarkers was significantly different compared with the other group of patients: mean age was 61.4 and 66.1 years, respectively (2-tailed *t* test, $P < .0001$). The group of patients who underwent biomarker analysis was also characterized by a higher proportion of women (39.3% vs. 16.6%; χ^2 test $P < .0001$), patients with adenocarcinoma (88.2% vs. 46.3%; χ^2 test $P < .0001$), and never-smokers (34.3% vs. 13.4%; χ^2 test $P < .0001$) (see Table 4 for absolute frequencies).

The percentage of patients with biomarker analysis was different among different geographical areas: the proportion of patients with EGFR mutation analysis was equal to 60.5% (n = 158) in the North, 74.8% (n = 77) in the center, and 45.2% (n = 80) in the South, Sardinia, and Sicily. Median time for obtaining the result of EGFR mutational analysis was 12 days (25-75 percentile, 7-18 days), being 11, 11, and 15 days in Northern, Central, and Southern Italy, respectively.

The timing of biomarker analysis with respect to administration of subsequent lines of treatment is shown in Figure 3. EGFR mutation status was known before first-line treatment in more than half of the patients.

Among 168 patients with known status of wild type EGFR expression at the beginning of second-line therapy, 112 (66.7%) received chemotherapy and 56 (33.3%) received a targeted agent (mostly erlotinib). Of 149 patients who received erlotinib as second-line therapy in clinical practice, EGFR mutational status was known in 62 cases: 8 patients had EGFR mutated tumors, and 54 were wild type.

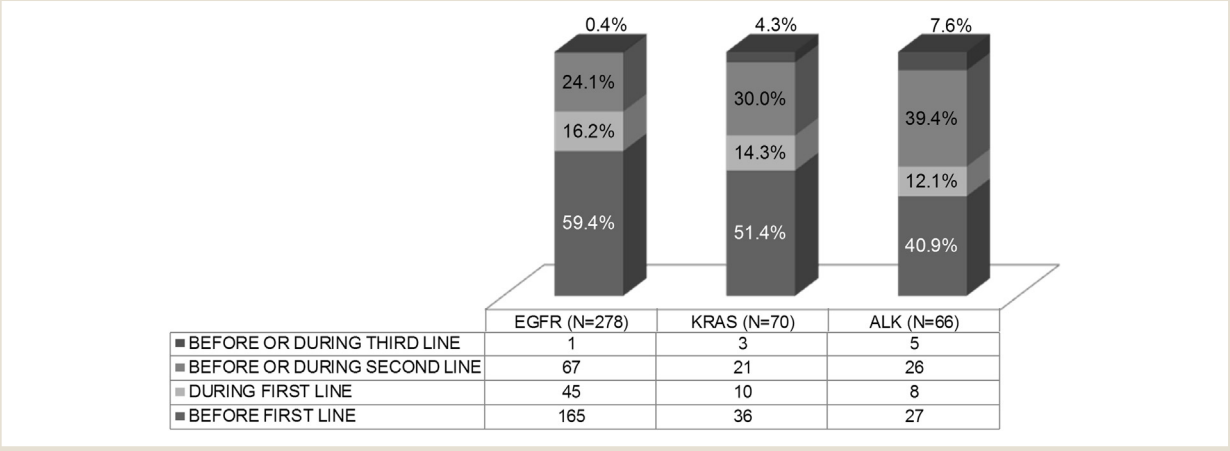
Among 56 patients with wild type EGFR at the beginning of third-line therapy, 32 (57.1%) received chemotherapy and 24 (42.9%) received a targeted agent (mostly erlotinib). Of 64 patients

Table 4 Characteristics of Patients With and Without Biomarker Analysis[a]

Characteristic	Patients Without Biomarker Analysis (n = 175)	Patients With Biomarker Analysis (n = 323)	*P*
Gender			<.0001
Male	146 (83.4%)	196 (60.7%)	
Female	29 (16.6%)	127 (39.3%)	
Age			<.0001
Mean ± SD	66.1 ± 9.3 Years	61.4 ± 10.7 Years	
Histology			<.0001
Adenocarcinoma	81 (46.3%)	285 (88.2%)	
Other	94 (53.7%)	38 (11.8%)	
Smoking Status at Diagnosis			<.0001
Never smoker[b]	22 (13.4%)	107 (34.3%)	
Former smoker	74 (45.1%)	127 (40.7%)	
Current smoker	68 (41.5%)	78 (25.0%)	
ECOG Performance Status at Diagnosis			.02
0-1	157 (94.0%)	295 (98.0%)	
2 or worse	10 (6.0%)	6 (2.0%)	

Analysis performed on patients with available information on biomarker analysis execution and considered characteristics.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor.
[a]EGFR mutation and/or KRAS mutation and/or ALK translocation.
[b]Less than 100 cigarettes in lifetime.

Figure 3 Timing of Biomarker Analyses (Patients With Not Computable Timing Are Excluded); EGFR, n = 37; KRAS, n = 13; ALK, n = 18)



	EGFR (N=278)	KRAS (N=70)	ALK (N=66)
BEFORE OR DURING THIRD LINE	1	3	5
BEFORE OR DURING SECOND LINE	67	21	26
DURING FIRST LINE	45	10	8
BEFORE FIRST LINE	165	36	27

Abbreviation: EGFR = Epidermal Growth Factor Receptor.

who received erlotinib as third-line therapy in clinical practice, EGFR mutational status was known in 29 cases: 5 patients had EGFR mutated tumors, and 24 had wild type tumors.

Discussion

In the present report, the results of the longitudinal phase of the LIFE study are reported. This is, to our knowledge, the most updated observational study performed in Italy in the setting of advanced NSCLC after failure of first-line treatment.

According to our results, a significant proportion of patients are considered for further active systemic treatment (chemotherapy or targeted agents), even after failure of second-line therapy. Furthermore, the LIFE study results document, for patients treated in routine clinical practice, a common use of biomarker analyses that up to a few years ago were used only for research purposes.

The LIFE study offers an overview of Italian clinical practice in advanced NSCLC management for a large number of patients. However, all these data should be considered with caution because of potential risks of selection bias, related to the enrollment of patients alive after first-line progression and to the site selection procedure. Furthermore, participating sites do not represent a random sample of all oncology and pulmonology Italian centers; nevertheless they were well distributed according to region and institution type. The fact clinicians were observed during their clinical practice might have changed their behavior, simply because they participated in the study (Hawthorne effect). However sites had to consecutively enroll patients; this procedure was aimed at obtaining a random sample and had a beneficial effect of reducing risk of patient selection. Moreover, on-site monitoring visits were performed to check source data. Finally the study focus was on advanced NSCLC patient management and not on a single drug. All of these contributed to mitigating risk of the Hawthorne effect.

Third-line chemotherapy is not supported by evidence from randomized trials, however, it is proposed to some patients in many institutions.[22-25] In the series of Italian patients described in this report, third-line treatment was received by 158 patients (40%) who completed a second-line therapy in clinical practice. Although erlotinib remains the only drug to have demonstrated efficacy in third-line setting, the proportion of patients receiving more than 2 lines of treatment has probably increased in recent years in clinical practice because of the availability of several drugs (cytotoxic drugs and targeted agents) showing activity in advanced NSCLC.[23-25] An earlier version of the European Society for Medical Oncology (ESMO) guidelines published in 2009[26] did not mention the opportunity of third-line treatment. However, the most recent version of the ESMO guidelines published in 2012[27] state that further treatment may be considered in patients after failure of second-line treatment, although the only evidence of efficacy has been shown for erlotinib. Clinical practice guidelines published by the American Society of Clinical Oncology in 2009 state that treatment with erlotinib may be recommended as third-line therapy for patients with PS of 0 to 3, who have not received previous erlotinib or gefitinib, although the data were considered insufficient to make a recommendation for or against using a cytotoxic drug as third-line therapy.[2] Similarly, guidelines published in 2011 by the Italian Association of Thoracic Oncology stated that erlotinib was the only drug approved for use in clinical practice as third-line treatment, and that there were no available trials designed to define the efficacy of third-line chemotherapy in advanced NSCLC.[5] In our series, erlotinib was used in 40.5% (n = 64) of patients receiving a third-line treatment, and the remaining subjects received third-line chemotherapy (single-agent in most cases). None of the cytotoxic drugs used have a specific, solid demonstration of efficacy as third-line treatment. However, our data document that oncologists still consider further chemotherapy for some patients with advanced NSCLC who have already experienced failure of 2 treatment lines but are still clinically fit. This common use of cytotoxic drugs in a third-line setting could be related to drug cost considerations, or could be related to the fact that many clinicians believe that erlotinib is not as effective in EGFR wild type patients as chemotherapy,

after the demonstration of strong interaction between efficacy of the drug and presence of EGFR mutation. Treatment options used in Italian clinical practice for patients with locally-advanced or metastatic NSCLC were evaluated, several years ago, by the observational SUN (Survey on the lUng cancer maNagement) study.[22] The SUN study aimed to describe the Italian clinical practice in the period between January 2007 and March 2008. With the exclusion of patients enrolled in clinical trials, approximately 80% of 987 newly diagnosed patients received a first-line treatment, 32% of them received a second-line and 7.3% a third-line treatment.[24] Of course, this proportion is not directly comparable with the proportion observed in the LIFE study (40%), because the SUN study started the observation from NSCLC diagnosis, and the cohort of patients enrolled in the LIFE study was clinically selected for receiving a second-line treatment.

In the LIFE study, information about selected biomarker analyses used in clinical practice was collected: EGFR mutation and ALK rearrangement, because of potential therapeutic implications, and KRAS mutation, which was commonly analyzed, although no clear implication for treatment choices has been demonstrated. Data on biomarker analyses performed in the cohort of patients enrolled in the LIFE study suggest that, in common practice, a relevant proportion of cases are tested for biomarkers. This could be a direct consequence of improvements in the understanding of tumor biology and the increasing importance of the identification of molecular predictive factors for drug response in patients with advanced NSCLC. In 2010, gefitinib became available in Italian clinical practice for any line of treatment (including first-line therapy), after the demonstration of efficacy compared with chemotherapy in this molecular subgroup of patients. In our series, the subgroup of patients undergoing biomarker analyses was clinically selected in terms of age (younger than patients without biomarker analyses), gender (greater proportion of women), histology (higher proportion of adenocarcinoma), and smoking history (greater proportion of never smokers). This is expected and consistent with the greater chances of detecting EGFR mutations in patients with the previously mentioned clinical characteristics[28] (notably, this differs from guidelines that suggest testing for EGFR mutations in all advanced NSCLC patients). More recently, crizotinib has demonstrated high efficacy in patients with tumors harboring ALK translocations.[20] During course of the LIFE study, gefitinib was available in Italian clinical practice for patients with the EGFR mutation (having been available since 2010), and crizotinib could be prescribed only in the context of clinical trials until it became available in April 2013. This should be taken into account when considering the low proportion of patients with information about ALK translocations in our series. Our data show a lower proportion of patients undergoing molecular analysis tests and a slightly longer time to obtain the results in Southern compared with Northern and central Italy; however, the situation is dynamic and improving rapidly.

In our series, a relevant proportion of biomarker analyses were performed before the administration of first-line treatment, as part of the baseline diagnostic phase. This is a direct consequence of the recent availability of targeted agents in clinical practice. Information about molecular features of the tumor is requested not only for scientific reasons, but for practical implications in clinical decision-making.

Conclusion

Although existing guidelines recognize that third-line chemotherapy is not supported by evidence from randomized trials, the results of the LIFE study suggest that use of further treatment for patients who have failed second-line treatment is not negligible, and that cytotoxic drugs are commonly used in this setting.

The LIFE study also documents the common use of biomarker analyses in clinical practice. Further improvements in the identification of molecular subgroups of advanced NSCLC patients and in the availability of targeted agents directed against molecular drivers will likely lead to an increase in the number of molecular analyses requested in this setting in the near future.

Clinical Practice Points

- Erlotinib is the only drug with evidence of efficacy as third-line treatment in patients with advanced NSCLC not eligible for further chemotherapy, and no cytotoxic agent has a specific, solid demonstration of efficacy as third-line therapy. However, several reports have shown that many oncologists consider the opportunity for further active treatment after failure of second-line therapy.
- Results of the LIFE cohort multicenter observational study show that the proportion of patients with advanced NSCLC who receive more than 2 treatment lines is not negligible in Italian clinical practice. Most patients who received a third-line of treatment were treated with a cytotoxic agent (single-agent in most cases, with vinorelbine, docetaxel, and gemcitabine as the most frequently used agents), and only a small proportion received erlotinib, the only drug approved in this setting. Biomarker analysis (EGFR mutation and ALK translocation) were performed as part of clinical practice in a relevant proportion of patients, generally performed at the time of diagnosis on diagnosis-available tissue.
- The proportion of patients receiving more than 2 lines of treatment in clinical practice will probably be higher, compared with some years ago. ESMO guidelines for the treatment of advanced or metastatic NSCLC published in 2012 reported that further treatment might be considered in patients after failure of second-line treatment, in patients with or without oncogene addicted tumors. Use of molecular analysis in clinical practice will become more frequent, along with the increase of available targeted agents and predictive biomarkers.

Acknowledgments

This study was sponsored by Boehringer Ingelheim, Italy. Scientific and technical coordination, data management, and statistical support were provided by Medidata.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Di Maio M, Lama N, Morabito A, et al. Clinical assessment of patients with advanced non-small-cell lung cancer eligible for second-line chemotherapy: a prognostic score from individual data of nine randomised trials. *Eur J Cancer* 2010; 46:735-43.

2. Azzoli CG, Baker S Jr, Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2009; 27:6251-66.
3. Felip E, Gridelli C, Baas P, Rosell R, Stahel R, Panel Members. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy: 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010. *Ann Oncol* 2011; 22:1507-19.
4. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 2.2012. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed January, 2013.
5. de Marinis F, Rossi A, Di Maio M, et al. Treatment of advanced non-small-cell lung cancer: Italian Association of Thoracic Oncology (AIOT) clinical practice guidelines. *Lung Cancer* 2011; 73:1-10.
6. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; 18:2085-103.
7. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. *J Clin Oncol* 2000; 18:2354-62.
8. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; 22:1589-97.
9. Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. *J Thorac Oncol* 2011; 6:64-70.
10. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small cell lung cancer. *N Engl J Med* 2005; 353:123-32.
11. Costanzo R, Piccirillo MC, Sandomenico C, et al. Gefitinib in non small cell lung cancer. *J Biomed Biotechnol* 2011; 2011:815269.
12. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; 361:947-57.
13. Han JY, Park K, Kim SW, et al. First-SIGNAL: First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers With Adenocarcinoma of the Lung. *J Clin Oncol* 2012; 30:1122-8.
14. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; 11:121-8.
15. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010; 362:2380-8.
16. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; 12:735-42.
17. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; 13:239-46.
18. Gridelli C, Ciardiello F, Gallo C, et al. First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial. *J Clin Oncol* 2012; 30:3002-11.
19. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010; 363:1693-703.
20. Di Maio M, Krzakowski M, Fougeray R, et al. Prognostic score for second-line chemotherapy of advanced non-small-cell lung cancer: external validation in a phase III trial comparing vinflunine with docetaxel. *Lung Cancer* 2012; 77:116-20.
21. Gridelli C, de Marinis F, Ardizzoni A, et al. Advanced non-small cell lung cancer management in patients progressing after first-line treatment: results of the cross-sectional phase of the Italian LIFE observational study. *J Cancer Res Clin Oncol* 2014 (in press).
22. Gridelli C, Ardizzoni A, Barni S, et al. Medical treatment choices for patients affected by advanced NSCLC in routine clinical practice: results from the Italian observational "SUN" (Survey on the lUng cancer maNagement) study. *Lung Cancer* 2011; 74:462-8.
23. Song Z, Yu Y, Chen Z, Lu S. Third-line therapy for advanced non-small-cell lung cancer patients: feasible drugs for feasible patients. *Med Oncol* 2011; 28(suppl 1):S605-12.
24. Girard N, Jacoulet P, Gainet M, et al. Third-line chemotherapy in advanced non-small cell lung cancer: identifying the candidates for routine practice. *J Thorac Oncol* 2009; 4:1544-9.
25. Asahina H, Sekine I, Horinouchi H, et al. Retrospective analysis of third-line and fourth-line chemotherapy for advanced non-small-cell lung cancer. *Clin Lung Cancer* 2012; 13:39-43.
26. D'Addario G, Felip E, ESMO Guidelines Working Group. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009; 20(suppl 4):68-70.
27. Peters S, Adjei AA, Gridelli C, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; 23(suppl 7):vii56-64.
28. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009; 361:958-67.

Supplemental Appendix 1

The LIFE Study Group

First Name	Surname	Affiliation	City
Paolo	Pedrazzoli	IRCCS Policlinico San Matteo	Pavia
Salvatore	Siena	Ospedale Niguarda Ca' Granda	Milano
Oscar	Alabiso	A.O.U. Maggiore della Carità	Novara
Domenico	Bilancia	Azienda Ospedaliera San Carlo	Potenza
Saverio	Cinieri	P.O. Antonio Perrino	Brindisi
Giacomo	Cartenì	AORN "A. Cardarelli"	Napoli
Gianpiero	Fasola	Azienda Ospedaliera Universitaria di Udine	Udine
Francesco	Ferraù	Ospedale San Vincenzo	Taormina
Michele	Milella	Istituto Regina Elena	Roma
Antonio	Contu	Ospedale Civile SS. Annunziata	Sassari
Dario	Giuffrida	Istituto Oncologico del Mediterraneo	Viagrande
Alfonso	Illiano	A.O.R.N. Monaldi	Napoli
Alberto	Ravaioli	Ospedale degli Infermi	Rimini
Alberto	Zaniboni	Fondazione Poliambulanza	Brescia
Anna	Bettini	Az. Osp. Ospedali Riuniti	Bergamo
Alberto	Caprioli	Spedali Civili di Brescia	Brescia
Flavia	Longo	Policlinico Umberto I	Roma
Giorgio	Cruciani	Ospedale di Lugo Umberto I	Lugo
Efisio	Defraia	Ospedale Oncologico Businico	Cagliari
Adolfo	Favaretto	Istituto Oncologico Veneto - IOV	Padova
Dino	Amadori	IRST di Meldola	Meldola
Mario	Clerico	Ospedale degli Infermi	Biella
Francesco	Di Costanzo	A.O.U. Ospedale Careggi	Firenze
Teresa	Gamucci	Ospedale S.S. Trinità	Sora
Michele	Caruso	Humanitas Centro Catanese di Oncologia	Catania
Stefano	Iacobelli	Ospedale SS Annunziata	Chieti Scalo
Graziella	Pinotti	Ospedale di Circolo e Fondazione Macchi	Varese
Daniele	Pozzessere	Ospedale Misericordia e Dolce AUSL4 di Prato	Prato
Evaristo	Maiello	Casa Sollievo della Sofferenza	San Giovanni Rotondo
Paolo	Marchetti	Azienda Ospedaliera Sant'Andrea	Roma
Rodolfo	Passalacqua	Azienda Istituti Ospitalieri	Cremona
Lorenzo	Pavesi	Fondazione S. Maugeri IRCCS	Pavia
Giampaolo	Tortora	Policlinico G.B. Rossi di Borgo Roma	Verona
Massimo	Aglietta	IRCC Istituto per la Ricerca e la Cura del Cancro	Candiolo
Roberto	Bianco	A.O.U. Federico II	Napoli
Alba	Brandes	Ospedale Bellaria	Bologna
Libero	Ciuffreda	Azienda Ospedaliera Città della Salute e della Scienza	Torino
Bruno	Daniele	Ospedale G. Rummo	Benevento
Claudio	Demichelis	Ospedale Unificato d'Imperia	Imperia
Sante	Romito	Az. Osp. Univ. Ospedali Riuniti	Foggia
Stefano	Tamberi	Ospedale degli Infermi	Faenza
Sandro	Barni	Ospedale Treviglio-Caravaggio	Treviglio
Fausto	Barbieri	Az. Osp. Univ. Policlinico	Modena
Monica	Giordano	Az. Osp. Sant' Anna	San Fermo della Battaglia
Sergio	Bracarda	Ospedale San Donato	Arezzo
Lucio	Crinò	Azienda Ospedaliera Perugia	Perugia
Nicola	Marzano	Ospedale San Paolo	Bari
Marco	Merlano	A.S.O. S. Croce e Carle	Cuneo
Gianmauro	Numico	Ospedale Regionale U. Parini	Aosta