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Abstract

Purpose

LIFE (non-small cell Lung cancer management In patients progressing after First-linE of treatment in the metastatic setting) is a multicentre Italian observational study, including a cross-sectional and a longitudinal phase, with the aim of describing the therapeutic approach in clinical practice for advanced non-small cell lung cancer (NSCLC) patients, progressing after first-line treatment.

Methods

In this paper, the cross-sectional phase is outlined, with the primary endpoint of describing the proportion of patients receiving second-line treatment among those progressed during or after first-line treatment according to clinical practice.

Results

From July 2011 to January 2012, 603 patients were enrolled and 541 (90 %) were evaluable. A total of 464 (86 %) patients received a second-line therapy outside clinical trials. Chemotherapy and targeted therapies were administered to 65 and 34 % of patients, respectively (1 % both). No tissue collection was required within the observational trial, and biomarkers analysis was performed at diagnosis or later in 314 patients (58 %). In details, activating epidermal growth factor receptor mutations were detected in 21 % of 311 evaluable patients, Kirsten rat sarcoma 2 viral oncogene homolog mutation in 22 % of the 77 evaluable patients and anaplastic lymphoma kinase translocations analysis was performed in 74 patients and resulted positive in 23 % of cases. These high proportions were probably due to enriched patient population tested.

Conclusions

These results showed a pattern of care for NSCLC second-line therapy which reflects international guidelines recommendations and current expected clinical practice. Interestingly, biomarkers analyses were performed in a higher percentage than expected.

Keywords

Chemotherapy NSCLC Observational Study Second-line Targeted therapy Biomarkers

Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 85 % of cases (Govindan et al. 2006). At diagnosis, more than 50 % of patients have advanced disease for which systemic therapy, especially platinum-based doublets, is still used reaching a plateau of effectiveness (Goffin et al. 2010).

Patients who receive first-line chemotherapy experience disease progression. Second-line chemotherapy with docetaxel, when compared with placebo or single-agent vinorelbine or ifosfamide, showed to improve survival in all NSCLC histologies (Shepherd et al. 2000; Fossella et al. 2000). Pemetrexed is approved for use only in non-squamous NSCLC being emerged, when compared with docetaxel, as the preferred option in this subgroup because of its more favourable toxicity profile (Hanna et al. 2004). After chemotherapy failure, second- or third-line erlotinib, a reversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), showed to improve survival and cancer-related symptoms, when compared with

placebo, being indicated for use in all histologies, and in both EGFR wild-type (wt) and mutated NSCLC (Shepherd et al. 2005).

Epidermal growth factor receptor (EGFR) activating mutations were identified as the most important factor for selecting NSCLC patients who might benefit from EGFR-TKIs therapy. One single point mutation in exon 21, the L858R, and a series of small in-frame deletions in exon 19 account for approximately 90 % of all EGFR mutations. EGFR mutations are more frequent in female patients as compared with male (38.7 vs. 10 %); in adenocarcinoma as compared with other histological types (29.4 vs. 1.8 %); in non-smokers as compared with current smokers or former smokers (45.8 vs. 7.1 %); and in East-Asians (33.4 %) as compared with non-East-Asian patients (5.5 %) (Normanno et al. 2006).

Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) is indicated as a key molecule for EGFR-regulated signal transduction pathways of cell proliferation. KRAS mutations in codons 12 or 13 have also been considered as responsible of resistance development to EGFR inhibitors. However, the results available are still controversial (Roberts et al. 2010; Ferté et al. 2010; Linardou et al. 2008).

Anaplastic lymphoma kinase (ALK) is a transmembrane receptor tyrosine kinase of the insulin receptor superfamily. About 2–7 % of patients with NSCLC have tumours with an inversion in the short arm of chromosome 2, which results in the fusion of exons 1–13 of the echinoderm microtubule-associated protein-like 4 (EML4) gene with exons 20–29 of the ALK gene, leading to the production of an EML4-ALK fusion tyrosine kinase, which is involved in cell proliferation, differentiation and anti-apoptosis (Soda et al. 2007). Crizotinib, an oral selective corresponding inhibitor, showed to improve survival when compared to second-line chemotherapy in ALK positive patients (Pfizer press 2012). ALK translocations, EGFR and KRAS mutations are usually mutually exclusive (Rossi and Galetta 2012).

Treatment options of locally advanced or metastatic NSCLC applied in Italian clinical practice were evaluated by the observational SUN study (Survey on the lUng cancer maNagement) reflecting the Italian clinical practice from January 2007 to March 2008 (Gridelli et al. 2011). Considering only treatments according to clinical practice, about 80 % of 987 newly diagnosed observed patients received a first-line treatment, 32 % of them received a second-line treatment and 7.3 % third-line treatment. The SUN study principal aim was investigating the therapeutic algorithm of patients from advanced NSCLC diagnosis, without providing information about biomarkers and its possible use as predictive factors. The observational LIFE study aims to describe management of the disease in clinical practice of advanced NSCLC patients from 60 Italian Oncology and Pneumology centres progressing after first-line treatment. More specifically, the primary aim of the cross-sectional phase, which is object of the present paper, is the description of second-line approaches, while among secondary endpoints there is the description of the clinical practice for biomarkers identification in terms of execution, results and patients' features.

Patients and methods

Study design and entry criteria

LIFE involved 60 Italian Oncology and Pulmonology centres chosen among those with necessary resources to conduct the study, and it consisted in a cross-sectional and a longitudinal phase. Cross-sectional observations were collected during the baseline visit and referred to the previous 6 months, longitudinal evaluations covered a 6-month follow-up period (Fig. 1). Patients aged 18 years or older, with histological or cytological stage IIIB–IV NSCLC diagnosis, with disease progression after first-line treatment according to clinical practice within 6 months prior to enrolment were consecutively enrolled with a competitive enrolment strategy. Patients had to sign the informed consent and privacy disclosure at the enrolment and receive at baseline any line of treatment after the first disease progression (second-line treatment or further) according to clinical practice or in a clinical trial setting or receiving best supportive care. The protocol was approved by the independent ethical committees of the participating institutions.

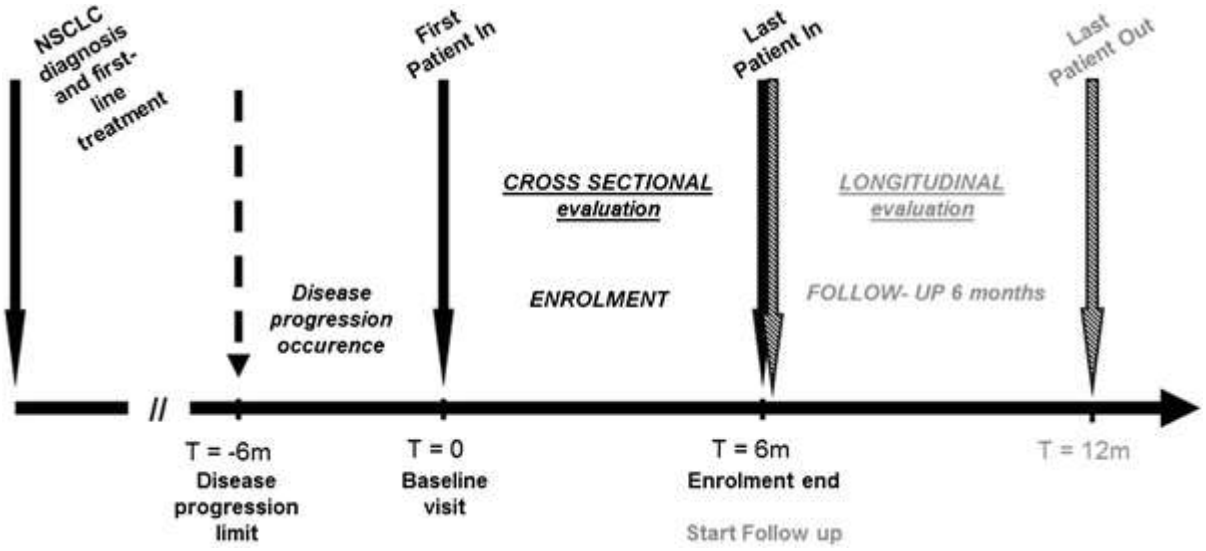

Fig. 1

Study diagram. (The *arrows* from $T = 0$ to $T = 6$ months delimit the period of patients enrolment lasting 6 months—cross-sectional phase of the study. The *dotted arrow* indicates the 6 months prior to baseline, during which the included patients must have experienced progression of disease following a first-line treatment. The *arrows* from $T = 6$ months to $T = 12$ months delimit the patients observation period lasting 6 months—longitudinal phase of the study)

Data collection and methods

The information requested as defined by the protocol was collected using an electronic data collection sheet. Patients underwent clinical examination at enrolment and then were followed for 6-month follow-up visit. Socio-demographics, NSCLC history, co-morbidities history, data relating to the different lines of treatment, mutational analysis of EGFR, KRAS and ALK translocations were recorded at baseline.

Second-line treatment was defined by the clinician as any chemotherapy and/or targeted therapy administered according to routine clinical practice or within a clinical trial subsequent to first-line progression. Patients were considered receiving best supportive care when they did not start any line of active treatment as defined above.

Sample size and statistical analysis

Here, we report data regarding the cross-sectional phase of the study.

Sample size was calculated according to available data (data from local centre database confirmed by Steering Committee members of the study) for the year 2009. The expected proportion of patients receiving second-line therapy out of patients treated with first-line was 27 %, whereas 19 % was the proportion of patients receiving third-line treatment out of those treated with second-line treatment. Assuming a sample size equal to 450, the two-sided confidence interval for the proportion using the large sample normal approximation was expected to be 27 ± 4.1 % (Dixon and Massey 1983). Considering about 10 % of not evaluable patients for this cross-sectional objective, 500 patients were planned to be enrolled. Larger sample size meant higher estimate precision.

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

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

Results

Characteristics of patients

A total of 603 patients referring to 60 Italian Oncology and Pneumology centres, well distributed among geographical areas (31 north, 11 centre, 18 south Italy) and types (30 hospitals, 11 university hospitals, 9 scientific hospitalization and care institutes, 8 hospital units, 2 other), were enrolled from July 2011 to January 2012. Five hundred and forty one of them (89.7 %) met the inclusion criteria with main reasons of patient exclusion being disease progression out of the requested timeframe (6.5 %) and first-line treatment not according to clinical practice (1.3 %). Table 1 shows patient characteristics at stage IIIB–IV NSCLC diagnosis and at baseline visit. The median time from diagnosis of stage IIIB–IV NSCLC to baseline visit was 9.86 months. Most of patients were male (*N* = 378–70 %), aged ≤70 years (*N* = 364–67 %), while 177 (33 %) were elderly (>70), the median age was 65 years. Three quarters of patients (*N* = 405) had stage IV, and adenocarcinoma was the histological type in 389 (72 %) subjects. PS (performance status) was 0–1 in 488 (90 %) patients, and important co-morbidities were present in 321 (59 %). Patients were smokers and former smokers in 30 % (*N* = 160) and 41 % (*N* = 221) of cases, respectively. Almost all patients performed computed tomography (CT) as a diagnostic tool, and approximately, in half of the cases cyto-histological diagnosis was performed through fibrobronchoscopy. While 61 (11 %) patients were asymptomatic, the most frequently observed cancer-related symptoms at diagnosis were cough (43 %), dyspnea (29 %), bone pain (18 %) and fatigue (11 %), followed by haemoptysis (7 %), weight loss (7 %), chest pain (6 %), fever (5 %), dysphonia (2 %), loss of appetite (2 %), neurological disorders (1 %), asthenia (1 %) and headache (1 %). Other symptoms were observed in 57 (11 %) patients, and data were not available in 46 patients (9 %) (Fig. 2).

Table 1

Baseline characteristics of patients (*n* = 541)

Parameter	**Number of patients (%)**
Patients characteristics	
Gender	
Male	378 (69.9)
Female	163 (30.1)
Age at study enrolment	
Median	65
Range	28–84
≤70 years	364 (67.3)
>70 years	177 (32.7)
Ethnicity	
Caucasian	539 (99.6)
African	2 (0.4)
Comorbidity at study enrolment (more than 1 possible)	
No important concomitant diseases	218 (40.3)
Cardiovascular disease	207 (38.3)
Metabolic disease	99 (18.3)
Lung disease	42 (7.8)
Renal disease	10 (1.9)
Liver disease	17 (3.1)
Neurological/psychiatric disease	31 (5.7)
Other	85 (15.7)

Parameter	Number of patients (%)
ECOG performance status	
0	241 (44.5)
1	247 (45.7)
2	18 (3.3)
3	1 (0.2)
Not available	34 (6.3)
Smoking status	
Current	160 (29.6)
Former	221 (40.9)
Never	136 (25.1)
Not available	24 (4.4)
Disease characteristics at stage IIIB–IV non-small cell lung cancer diagnosis	
Stage	
IIIB	136 (25.1)
IV	405 (74.9)
Histotype	
Adenocarcinoma	389 (71.9)
Squamous	93 (17.2)
Large cell	12 (2.2)
Not otherwise specified	21 (3.9)
Other	26 (4.8)
Main non-invasive diagnostic procedures (more than 1 possible)	
Computed tomography	511 (94.5)
Chest X-ray	193 (35.7)
Positron emission tomography	184 (34.0)
Bone scan	107 (19.8)
Main invasive diagnostic procedures (more than 1 possible)	
Bronchoscopy	277 (51.2)
CT guided pulmonary biopsy	273 (50.5)
Thoracotomy	35 (6.5)
Thoracoscopy	29 (5.4)
Mediastinoscopy	6 (1.1)

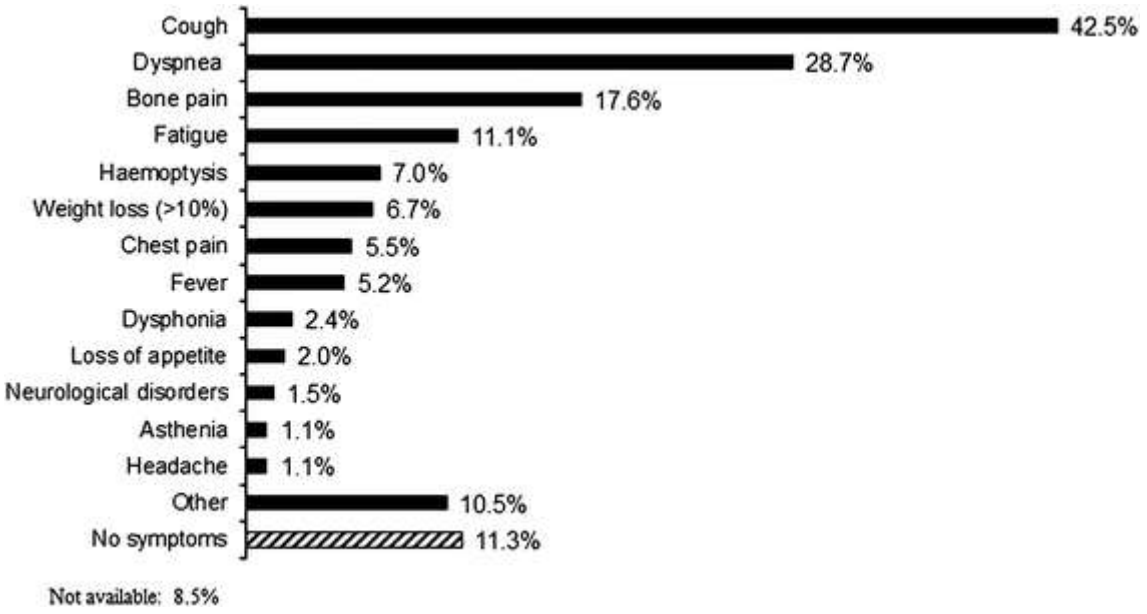

Fig. 2

Patient's symptoms at diagnosis. A *bar graph* displays the percentage of cancer-related symptoms at diagnosis

Biomarkers analysis

Biomarkers analysis was performed from NSCLC diagnosis to baseline visit in 314 patients (58 %): 311 EGFR, 77 KRAS and 74 ALK. The main characteristics of these patients were as follows: median age 62 years (younger than general patients population), 60 % male, PS 0–1 in 98 % of patients (for patients with this characteristic available), adenocarcinoma 89 %, former or never smoker in 40 and 34 % of cases, respectively. Before starting second-line therapy, EGFR mutational status was already evaluated in 274, KRAS in 68 and ALK translocation in 60 patients.

Among 311 patients with EGFR analysis performed from diagnosis to baseline, activating EGFR mutations were detected in 21 % (*N* = 65) of cases (18 % with deletions of exon 19 or L858R) with a median turnaround time (TAT) of 12 days (11 days for the north and centre of Italy, and 15 days for the south). In 84 % of cases, the request for biomarkers analysis was performed by the Oncologist. The request was by routine in 33 % of cases and influenced by histology (mostly adenocarcinoma) in 58 % of cases, smoking habit in 23 % and gender in 17 %. The laboratory conducting the analysis was internal to the hospital in 55 % (*N* = 171) of cases (69 % in the centre of Italy, 61 % in the north and 28 % in the south) with the analysis performed on a histological sample in most cases (*N* = 254) and mainly from lung primary tumours (*N* = 179). Polymerase chain reaction (*N* = 110) and direct sequencing (*N* = 80) (*N* = 54 data not available) were the most frequent techniques applied.

KRAS mutations were revealed in 17 (22 %) of the 77 evaluable patients with a median TAT of 12 days (12 days in the north, 14 days in the centre and 28.5 days in the south of Italy).

ALK translocations analysis was performed in 74 patients and resulted present in 17 (23 %) of them with a median TAT of 8 days (8 days in the north, 8.5 days in the centre and 18.5 days in the south of Italy) (Table 2).

Table 2

Summary of biomarkers analyses from NSCLC diagnosis to baseline visit

Biomarkers	Total	North of Italy	Centre of Italy	South of Italy
EGFR				

Biomarkers	Total	North of Italy	Centre of Italy	South of Italy
No.pts	311	158	77	76
Deletions exon 19[a,]*	42 (13.5)	25 (15.8)	9 (11.7)	8 (10.5)
L858R[a,]*	16 (5.1)	13 (8.2)	3 (3.9)	0 (0.0)
Others[a,]*	13 (4.2)	10 (6.3)	1 (1.3)	2 (2.6)
Median TAT (days)	12	11	11	15
KRAS				
No.pts	77	49	21	7
Mutations*	17 (22.1)	11 (22.5)	3 (14.3)	3 (42.9)
Median TAT (days)	12	12	14	28.5
ALK				
No.pts	74	40	24	10
Translocations*	17 (23.0)	7 (17.5)	9 (37.5)	1 (10.0)
Median TAT (days)	8	8	8.5	18.5

NSCLC non-small cell lung cancer, *EGFR* epidermal growth factor receptor, *KRAS* Kirsten rat sarcoma 2 viral oncogene homolog, *ALK* anaplastic lymphoma kinase, *TAT* turnaround time

* N (%)

[a]More than 1 type of EGFR mutation possible

First-line therapy

Chemotherapy

First-line chemotherapy was administered to 506 (94 %) patients (4 % with targeted therapy). Radiotherapy was also administered in combination with chemotherapy in 26 % of patients. Within the group of patients receiving chemotherapy, 50 (10 %) were treated with a single agent for a median of 5 cycles (IQR 3–6; 6 % gemcitabine, 1 % vinorelbine, 1 % docetaxel, 2 % other agents including carboplatin and pemetrexed) and 456 (90 %) with combination chemotherapy for a median of 5 cycles (IQR 4–6; 44 % platinum–pemetrexed, 31 % platinum–gemcitabine). In 13 % of patients, chemotherapy was delayed, and in 11 % of cases, chemotherapy doses were adapted due to safety concerns.

Almost all (97 %) adult patients received a platinum-based combination, while this percentage was lower (75 %) in elderly patients (*p* value <0.0001). The percentage of patients discontinuing treatment was similar between the two age groups (*p* value = 0.431), while significant differences were observed in dosage delay (10 vs. 19 % in elderly; *p* value = 0.004) and modification (15 vs. 24 %; *p* value = 0.024).

Targeted therapy

A total of 58 (11 %) patients received first-line targeted therapy alone or with chemotherapy. Gefitinib was administered to 32 (6 %) patients with a median duration of treatment of 6.4 months (IQR 4.1–9.4). Among them, 25 had activating EGFR mutations (the remaining 7 were not investigated for EGFR status), corresponding to 78 % of all patients with EGFR-activating mutations known before first-line treatment start. Twenty-eight patients discontinued gefitinib, while the dose was delayed in 6 cases. Bevacizumab was administered in combination mainly with carboplatin–paclitaxel or cisplatin–gemcitabine to 21 (4 %) patients with a median duration of treatment of 3.6 months (IQR 2.5–10.6). Bevacizumab was discontinued in 11 patients, and in one case, the dose was delayed. Erlotinib was administered to 5 (1 %) patients, one of which EGFR wild-type while the others were not investigated for EGFR status, with a median duration of 20.3 months (IQR 2.2–23.1). Erlotinib was discontinued in 4 patients, and the dose was delayed in 1 patient (Table 3).

Table 3

Summary of the main first-line therapies (*n* = 541)

Therapy	**Number of patients (%)**
Combination regimens (*n* = 456–84.3 %)	
Cisplatin/pemetrexed	163 (30.1)
Cisplatin/gemcitabine	86 (15.9)
Carboplatin/gemcitabine	70 (12.9)
Carboplatin/pemetrexed	60 (11.1)
Carboplatin/paclitaxel	30 (5.5)
Cisplatin/docetaxel	15 (2.8)
Carboplatin/vinorelbine	8 (1.5)
Cisplatin/vinorelbine	7 (1.3)
Carboplatin/docetaxel	3 (0.6)
Docetaxel/gemcitabine	2 (0.4)
Gemcitabine/vinorelbine	2 (0.4)
Cisplatin/gemcitabine/pemetrexed	2 (0.4)
Cisplatin/pemetrexed/vinorelbine	1 (0.2)
Cisplatin/gemcitabine/paclitaxel	1 (0.2)
Cisplatin/docetaxel/vinorelbine	1 (0.2)
Carboplatin/gemcitabine/pemetrexed	1 (0.2)
Single-agent chemotherapy (*n* = 50–9.2 %)	
Gemcitabine	31 (5.7)
Pemetrexed	7 (1.3)
Vinorelbine	6 (1.1)
Docetaxel	3 (0.6)
Cisplatin	1 (0.2)
Carboplatin	1 (0.2)
Targeted therapies (*n* = 58–10.7 %)	
Gefitinib	32 (5.9)
Bevacizumab in combination with chemotherapy (mainly plus CBDCA + PAC or CDDP + GEM)	21 (3.9)
Erlotinib	5 (0.9)

CBDCA carboplatin, *PAC* paclitaxel, *CDDP* cisplatin, *GEM* gemcitabine

Bevacizumab combined with chemotherapy was administered to 5 % (*N* = 20) of patients aged ≤70 years and 1 % (*N* = 1) of elderly patients ($p = 0.020$). No age differences were reported in terms of therapy discontinuation, delay or dose modification.

Overall, first-line treatment reported <1 % of complete response, 19 % partial response and 27 % stable disease. The median time to progression was 6.11 months (IQR 3–9).

Second-line therapy

This was the main endpoint of the cross-sectional phase of the LIFE study. A total of 62 (11 %) patients were included in second-line clinical trials, and 15 (3 %) received only best supportive care. Among 464 (86 %)

patients receiving second-line treatment outside clinical trials, 36 % were aged >70 years, 81 % had a good ECOG PS (0–1), 24 % were never smoker and 21 % current smoker. Chemotherapy, targeted therapy or both were administered to 301 (65 %), 160 (34 %) and 3 (1 %) patients, respectively. Palliative radiotherapy was administered in combination with systemic therapy in 11 % of patients. No differences in terms of drug choice were reported between the two age groups.

A doublet was used in 63 (14 %) subjects, while 241 (52 %) received a monotherapy. Docetaxel was the most common single-agent chemotherapy (25 %), followed by pemetrexed (15 %), gemcitabine (6 %) and vinorelbine (5 %). Platinum plus pemetrexed (4.5 %) and platinum plus gemcitabine (4 %) were the most frequently used second-line doublets. Erlotinib was prescribed to 149 (32 %) patients and 9 received gefitinib (Table 4).

Table 4

Summary of the main second-line therapies outside clinical trials (*n* = 464)

Therapy	**Number of patients (%)**
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 regimens (*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)
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 plus CBDCA + PAC	3 (0.6)

CBDCA carboplatin, *PAC* paclitaxel

Discussion

The present paper reports the results of the cross-sectional phase of the LIFE study. This is, to our knowledge, the most updated first observational study performed in Italy in this setting, including also information about biomarkers analyses of EGFR, KRAS mutations and ALK translocations. Evidence that 86 % of patients received a second-line treatment outside clinical trials can indicate that oncologists and patients perceive treatment outcomes for advanced NSCLC as having improved, despite the poor prognosis.

On the other side, this is a demonstration of a good application of Guidelines, despite the aggressiveness of the disease. In the SUN study, 32 % of previously treated patients received second-line therapy in clinical practice (71 % chemotherapy, mainly single-agent pemetrexed or docetaxel, and 29 % erlotinib) (Gridelli et al. 2011). Only 8 % of patients receiving second-line therapy in the SUN study were enrolled in clinical trials. The participating centres in the SUN and LIFE studies are comparable and well distributed by region and institution type (academic centres, national cancer institutes, general hospitals and peripheral centres). The difference observed in the percentage of patients receiving second-line treatment could be attributable to the different period of observation. The higher percentage of EGFR-TKIs therapy (34 % of both erlotinib and gefitinib) resulting from the LIFE study is probably due to a more careful search and detection of EGFR-activating mutations. The two trials also differ in terms of patients' selection: the SUN study enrolled patients at the time of NSCLC diagnosis, whereas the LIFE trial recruited patients only if alive after first-line progression.

Other observational studies reported data regarding the characteristics of second-line approaches in patients with recurrent NSCLC (Bischoff et al. 2010; Moro-Sibilot et al. 2010; Vergnenegre et al. 2012). The period of observation was prior to that reported in the LIFE study, and this does not allow for good quality comparisons. However, our study shows that the management of second-line treatment for NSCLC patients in routine clinical practice was generally consistent with the International and National treatment recommendations and guidelines and licensed indications of the drugs at study time (Felip et al. 2011; Azzoli et al. 2011; de Marinis et al. 2011).

Docetaxel, pemetrexed (only for non-squamous histology) and erlotinib account for second-line treatment of 72 % of patients. The high rate of docetaxel as second-line choice seems to be influenced by the regimen administered as first-line treatment. In fact, platinum–pemetrexed was the treatment of choice for first-line therapy, being adenocarcinoma the most frequently reported histological subtype and 59 % of patients suffering by severe co-morbidities, mainly cardiovascular, which could contraindicate the use of bevacizumab-based regimens. Among patients treated with second-line therapy, 14 % received combination chemotherapy despite failure to prove its superiority over single-agent treatment (Di Maio et al. 2009). Erlotinib was still less used than chemotherapy in second-line probably because of the oncologist preference for chemotherapy based on an unproved perception that chemotherapy works better than erlotinib particularly in smokers, squamous histology tumours and EGFR wt.

Unfortunately, in our data only 11 % of patients were enrolled in clinical trials, underlining the lack of an adequate number of studies addressing this issue as opposed to studies performed on first-line treatment, together with the difficulty to find adequate patients who fulfil inclusion criteria for second-line clinical trials.

While significant differences were observed in first-line treatment choice, in second-line setting elderly patients received the same type of treatment and drug of their younger counterpart.

Biomarkers analyses were performed for 58 % of enrolled patients. This percentage is higher than that reported by some randomized trials (Mok et al. 2009; Gridelli et al. 2012) performed at a time when there was still awareness of the importance of EGFR. This might be due also to the fact that the LIFE study considers only patients alive after first-line progression. However, this aspect may also emphasize that physicians pay more attention to diagnostic invasive tools to obtain not only a precise diagnosis but also biomarkers characterization. The percentage of EGFR mutations and ALK translocations reported in our series (21 and 23 %, respectively) was higher than that reported in the literature, but this was probably due to the clinical selection of patients (a large number of patients tested were never smokers and with adenocarcinoma histology) mainly for cost concerns of biomarkers assessment. Indeed, EGFR mutation was tested in an enriched patient population including 89.1 % of adenocarcinoma and 34.4 % of never smokers. Similarly, patients tested for ALK translocation had adenocarcinoma in 89.2 % of cases and were never smokers in 41.4 %. A discrepancy between the north, centre and south of Italy for biomarkers analyses is still present: this might be due to the fact that the south of Italy registered the lowest percentage of adequate amount of tumour tissue available for biomarkers analyses and the lowest percentage of centres performing tests together with the longest waiting time for results.

The LIFE study offers an overview of the Italian clinical practice in advanced NSCLC management over a high number of patients. However, all these data should be considered with caution due to potential risks of

selection bias, related to the enrolment of patients alive after first-line progression and to the sites selection procedure. Participating sites do not represent a random sample of all Oncology and Pulmonology Italian centres; nevertheless, they resulted to be well distributed by region and institution type.

In conclusion, the results of LIFE study provide valuable information about general population of patients, disease characteristics and treatment choices, prescribing patterns for patients receiving second-line treatment for NSCLC in routine clinical practice in Italy.

The study reflects an update on clinical practice towards a more tailored therapy and patient management from the last observational study, according to new therapeutic choices (in first- and second-line) and diagnostic tools. These results showed a pattern of care for second-line therapy which reflects the recommendations of International guidelines and the current expected clinical practice.

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Conflict of interest

The authors declare to have full control of all primary data, and they agree to allow the journal to review their data if requested. Authors declare the following conflict of interest: Gridelli Cesare, Grossi Francesco had received advisory/speaker honoraria and/or research funding from Boehringer Ingelheim Italy. de Marinis Filippo has received advisory/speaker honoraria and/or research funding from Boehringer Ingelheim Italy and Roche. Ardizzoni Andrea has received advisory/speaker honoraria and/or research funding from Boehringer Ingelheim Italy, Glaxo Smith-Kline, Eli Lilly, Pfizer, Pierre Fabre, Daiicki-Sankyo. Novello Silvia, Cortinovis Diego had received advisory/speaker honoraria and/or research funding from Boehringer Ingelheim Italy, Roche, Astra Zeneca, Eli Lilly. The following authors declare no conflict of interest instead: Cappuzzo Federico, Favaretto Adolfo, Bettini Anna, Siena Salvatore, Caprioli Alberto, Iurlaro Monica, Fontanini Gabriella, Santo Antonio, Lorusso Vito, Galetta Domenico.

Ethical standard

This study was approved by appropriate ethics committees and was therefore performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent

All persons gave their informed consent prior to their inclusion in the study.

Appendix: The LIFE study team

Filippo	De Marinis	AO San Camillo Forlanini	Roma
Cesare	Gridelli	A.O.R.N. San Giuseppe Moscati	Avellino
Antonio	Santo	Gruppo Interdisciplinare Veronese Oncologia Polmonare, AOUI	Verona
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