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BE-POSITIVE: Beyond progression after tyrosine kinase inhibitor in EGFR- positive non small cell lung cancer patients. Results from a multicenter Italian observational study

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UNIVERSITÀ DEGLI STUDI DI TORINO

Questa è la versione dell'autore dell'opera:

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BE-POSITIVE: Beyond progression after tyrosine kinase inhibitor in EGFR- positive non small cell lung cancer patients: Results from a multicenter Italian observational study

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Highlights

- EGFR-TKIs first line treatment evidences impressive objectives response rates.
- After 9–12 months acquired resistance to EGFR-TKIs arises.
- No optimal therapy has been established beyond EGFR-TKIs progression.
- This multicenter study describes patients who progressed to EGFR-TKIs.
- Treatments, efficacy and safety beyond EGFR-TKIs progression have been described.

Abstract

Objectives

Non-small-cell-lung-cancer (NSCLC) patients harbouring epidermal growth factor receptor (EGFR) mutations develop drug resistance after 9–12 months of EGFR tyrosine kinase inhibitors (TKIs) therapy pointing out the issue of the second-line treatment choice.

Materials and methods

From June 2009 until May 2013 patients affected by advanced NSCLC harbouring EGFR mutations receiving first-line TKI were collected mainly retrospectively in 24 Italian Centers. Primary objective was to describe the percentage of EGFR mutated patients receiving second-line therapy after progression to first-line EGFR-TKIs assessing the type, the activity in terms of objective response rate (ORR), efficacy in terms of progression free survival (PFS) and overall survival (OS), and safety of second-line treatment. Secondary objective was to describe the efficacy of first-line EGFR-TKIs.

Results

312 patients were included. Most of them were females (203, 65.1%), never smokers (200, 64.1%), with adenocarcinoma histology (290, 92.9%). The most common mutations were EGFR exon 19 deletion and L858R, detected in 186 and 97 cases (59.6% and 31.1%), respectively. At data cut-off, 274 patients (95.1%) received any second-line treatment (including best supportive care or local treatments only). A total of 163 patients received second-line systemic therapy with an ORR of 20.9% (95% CI:14.62–27.10), a median PFS and OS of 4.7 (95% CI:3.81–5.26) and 24.5 (95% CI:21.65–27.37) months, respectively. Grade 3–4 hematological and non-hematological toxicities

were reported in 9% and 6.3% of 144 patients treated with chemotherapy while non-hematological toxicity was reported in 4 cases of the 17 patients receiving second-line target agents.

Conclusions

BE-Positive is the first multicenter observational study reporting outcomes of therapies in a “real-life Caucasian EGFR-mutated population”, highlighting the need of further researches about new treatment strategies in this setting.

Abbreviations

- ESMO, European Society for Medical Oncology;
- ASCO, American Society of Clinical Oncology;
- ECOG, Eastern Cooperative Oncology Group

Keywords

- Non small cell lung cancer;
- EGFR mutation;
- EGFR tyrosine kinase inhibitors;
- First line;
- Second line;
- Acquired resistance

1. Introduction

Epidermal growth factor receptor (EGFR) activating mutations are diagnosed in approximately 11–18% of Caucasian patients and 50% of Eastern Asian ones affected by advanced non-small-cell-lung-cancer (NSCLC), mainly in the adenocarcinoma histotype [1] and [2].

Several randomized trials investigated an EGFR-tyrosine kinase inhibitor (TKI) (gefitinib, erlotinib, icotinib or afatinib) versus platinum-based chemotherapy, as first-line treatment of patients with advanced NSCLC harbouring activating EGFR mutations. These trials were mostly based on Asian populations, with few exceptions, such as the EURTAC trial which was entirely performed in European Countries, LUX-LUNG 3 which included patients from 25 centers worldwide with about 28% of Caucasian patients or the phase IV IFUM study which enrolled Caucasian patients only. All of them showed impressive objective response rates (ORRs) and prolonged progression-free survivals (PFSs) [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14] and [15].

Despite the initial response, after a median of 9–12 months, an acquired resistance to first-line EGFR-TKI arises, pointing out the issue of the second-line treatment choice. In 50–60% of cases this acquired resistance is due to the onset of an EGFR mutation of resistance (T790M), against which third-generation EGFR-TKIs are currently investigated [16], [17], [18] and [19]. For the remaining 40–50% of patients in which the acquired resistance is due to different intrinsic mechanisms, at present, no optimal therapy has been established for daily clinical practice. The ESMO

guidelines and the most recent ASCO ones suggest combination cytotoxic chemotherapy as second-line for patients with sensitizing EGFR mutations who did not respond to first-line EGFR-TKI, while patients who received a first-line EGFR-TKI and experienced disease progression after an initial response may be switched to chemotherapy or another EGFR-TKI as second-line therapy [20] and [21].

With the purpose to describe physician's choices and outcomes of second-line treatment in EGFR mutated patients who progressed to first-line TKI, we performed the BE-POSITIVE trial (Beyond progression after tyrosine kinase inhibitor in Egfr-POSITIVE NSCLC patients), a multicenter Italian observational study in a national context and in a "*real life Caucasian population*".

2. Materials and methods

2.1. Study design and patients

This multicentre study included NSCLC patients treated with first-line EGFR TKI: data of patients starting treatment from June 2009 to April 2012 were retrospectively included, while patients who started treatment from June 2012 to May 2013 were prospectively enrolled.

Patients' records were collected by each institution, centrally stored and analysed by the Coordinating Center.

Main inclusion criteria were: histological or cytological confirmed stage IIIB-IV NSCLC diagnosis by the AJCC Staging Manual 7th edition, presence of activating EGFR mutation on FFPE (formalin fixed and paraffin embedded) or cytological specimens obtained by either surgical or needle biopsy/aspiration procedures, locally sequenced for mutational analysis. All patients received first-line EGFR-TKI without any prior systemic chemotherapy, biological or immunological treatments.

For each patient, baseline information was collected about age, gender, ECOG performance status (PS) and smoking habit. Never smokers were defined as patients who had never smoked or smoked fewer than 100 cigarettes in their lifetime; former smokers were defined as patients who had a smoking history of at least 100 cigarettes in their lifetime and who, at the time of the enrolment, were not smoking anymore since at least six months; current smokers were those who reported smoking at least 100 cigarettes in their lifetime and who, at the time of survey, smoked either every day or sometimes.

Tumor-related features were evaluated in terms of stage at diagnosis, metastatic sites, histology and type of EGFR mutation.

The study protocol was approved by the Institutional Review Board of the Coordinating Center: Thoracic Oncology Unit, Department of Oncology, San Luigi Gonzaga University Hospital (Orbassano-Turin, Italy) and by all participating centers.

2.2. Treatments and assessments

For each patient, information was collected about first-line EGFR-TKI and second-line treatment choices: for both, treatment duration, toxicity (grade 1–2 and grade 3–4 cutaneous, gastro-intestinal, hematological, according to Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) and dose reductions were recorded.

First-line treatment with EGFR-TKIs included only drugs reimbursed in Italy for this setting of advanced NSCLC bearing activating EGFR mutations, at the time of observation: gefitinib was taken orally at a dosage of 250 mg/day and erlotinib, since it became available for this indication (April 2013), was prescribed at the standard dose of 150 mg/day [22].

Timing and sequence of subsequent treatments were at physicians' discretion.

Computed tomography (CT) scans of chest, upper abdomen (including liver and adrenal glands) and brain, were obtained before each line of treatment, following routine clinical practice, and thereafter to evaluate the response, its duration and progression. Best ORR was recorded for first and subsequent lines of treatment.

The primary objective was to describe the percentage of EGFR mutated patients receiving second-line therapy after progression to first-line EGFR-TKIs assessing the type, activity (in terms of ORR), efficacy (in terms of PFS and OS) and safety of second-line treatment. Secondary objective was the description of the efficacy of first-line EGFR-TKIs in this real life setting.

Progressive disease (PD), stable disease (SD), partial response (PR) and complete response (CR), were defined by tumor assessments from radiological tests according to RECIST criteria (Response Evaluation Criteria in Solid Tumors version 1.1); patients who were not reassessed for response due to worsening of PS were considered as no responders.

2.3. Statistical analysis

For both first- and second-line, PFS was measured from the first day of treatment to the date of first objective or clinical sign of PD, death (whichever came first) or to the date of last follow-up visit for patients censored without progression. OS was measured from the first day of TKI treatment to the date of death or the date of last follow-up visit for patients who were still alive. PFS and OS data were estimated by the Kaplan-Meier method. For the descriptive analysis, categorical data were summarized by the frequencies and percentages and the continuous covariates were indicated with median, range and numbers of observations.

3. Results

3.1. Accrual and patient characteristics

From June 2009 to April 2012, data of 225 NSCLC patients who started first-line EGFR-TKI were retrospectively collected; in addition, from June 2012 to May 2013, 87 NSCLC patients were prospectively observed in 24 Italian Hospitals, for a total of 312 cases (Fig. 1).

Fig. 1.

Be-POSITIVE Patients' CONSORT flow diagram.

Baseline characteristics of patients enrolled are summarized in Table 1. Disease characteristics of the study population are reported in Table 2.

Table 1.

Demographics.

	Erlotinib n = 24	Gefitinib n = 288	Total EGFR-TKIs n = 312
	N(%)	N(%)	N(%)
Age			
Median (years)	63.5	68.5	68.0
Range (years)	(50.0–78.0)	(32.7–87.6)	(32.7–87.6)
<70	19 (79.2)	162 (56.3)	181 (58.0)
>=70	5 (20.8)	125 (43.4)	130 (41.7)
Missing	0 (0.0)	1 (0.3)	1 (0.3)
Gender			
Females	18 (75.0)	185 (64.2)	203 (65.1)
Males	6 (25.0)	103 (35.8)	109 (34.9)

	Erlotinib n = 24	Gefitinib n = 288	Total EGFR-TKIs n = 312
	N(%)	N(%)	N(%)
ECOG performance status at diagnosis			
0	7 (29.2)	120 (41.7)	127 (40.7)
1	17 (70.8)	125 (43.4)	142 (45.5)
2	0 (0.0)	36 (12.5)	36 (11.5)
3	0 (0.0)	6 (2.1)	6 (1.9)
4	0 (0.0)	1 (0.3)	1 (0.3)
Smoking habit			
Never	17 (70.8)	183 (63.5)	200 (64.1)
Former	7 (29.2)	88 (30.6)	95 (30.4)
< = 10 pack/years	2 (8.3)	32 (11.1)	34 (10.9)
> 10 pack/years < = 20	1 (4.2)	17 (5.9)	18 (5.8)
> 20 pack/years < = 30	3 (12.5)	4 (1.4)	7 (2.2)
> 30 pack/years < = 40	0 (0.0)	11 (3.8)	11 (3.5)
> 40 pack/years	0 (0.0)	21 (7.3)	21 (6.7)
Unknown	1 (4.2)	3 (1.1)	4 (1.3)
Current	0 (0.0)	15 (5.2)	15 (4.8)
< = 10 pack/years	0 (0.0)	2 (0.6)	2 (0.6)
> 10 pack/years < = 20	0 (0.0)	4 (1.4)	4 (1.3)
> 20 pack/years < = 30	0 (0.0)	2 (0.6)	2 (0.6)
> 30 pack/years < = 40	0 (0.0)	3 (1.1)	3 (1)

	Erlotinib n = 24	Gefitinib n = 288	Total EGFR-TKIs n = 312
	N(%)	N(%)	N(%)
>40 pack/years	0 (0.0)	4 (1.4)	4 (1.3)
Unknown	0 (0.0)	2 (0.6)	2 (0.6)

Table 2.

Disease characteristics.

	Erlotinib n = 24	Gefitinib n = 288	Total EGFR-TKIs n = 312
	N(%)	N(%)	N(%)
Stage at diagnosis			
IA	0 (0.0)	5 (1.7)	5 (1.6)
IB	0 (0.0)	8 (2.8)	8 (2.6)
IIA	3 (12.5)	6 (2.1)	9 (2.9)
IIB	0 (0.0)	4 (1.4)	4 (1.3)
IIIA	2 (8.3)	23 (8.0)	25 (8.0)
IIIB	2 (8.3)	16 (5.6)	18 (5.8)
IV	16 (66.7)	226 (78.5)	242 (77.6)
NC	1 (4.2)	0 (0.0)	1 (0.3)
Site of metastasis^a			
Lung	9 (37.5)	133 (46.2)	142 (45.5)
Bone	12 (50.0)	115 (39.9)	127 (40.7)
Lymph nodes	1 (4.2)	108 (37.5)	109 (34.9)

	Erlotinib n = 24	Gefitinib n = 288	Total EGFR-TKIs n = 312
	N(%)	N(%)	N(%)
Pleura	6 (25.0)	78 (27.1)	84 (26.9)
Brain	4 (16.7)	57 (19.8)	61 (19.6)
Liver	3 (12.5)	44 (15.3)	47 (15.1)
Adrenal cortex	2 (8.3)	23 (8.0)	25 (8.0)
Spleen	0 (0.0)	3 (1.0)	3 (1.0)
Kidney	0 (0.0)	2 (0.7)	2 (0.6)
Histotype			
Adenocarcinoma	23 (95.8)	267 (92.7)	290 (92.9)
Adenosquamous carcinoma	0 (0.0)	2 (0.7)	2 (0.6)
Large cell carcinoma	1 (4.2)	5 (1.7)	6 (1.9)
Not otherwise specified	0 (0.0)	4 (1.4)	4 (1.3)
Sarcomatoid carcinoma	0 (0.0)	1 (0.3)	1 (0.3)
Squamous cell carcinoma	0 (0.0)	8 (2.8)	8 (2.6)
Missing	0 (0.0)	1 (0.3)	1 (0.3)
EGFR mutation			
Del 19	16 (66.6)	170 (59.0)	186 (59.6)
L858R	4 (16.7)	93 (32.3)	97 (31.1)
Uncommon mutations	4 (16.7)	25 (8.7)	29 (9.3)

a

Frequencies of site of metastasis are not cumulative frequencies.

The most frequent EGFR mutations were exon 19 deletion and L858R mutation in exon 21 evidenced in 186 and 97 patients, respectively (59.6% and 31.1%). In 29 patients (9.3%) uncommon mutations (classified according to COSMIC descriptions) were detected. However this specific subgroup will be described in a separate publication.

3.2. Second-line treatment characteristics

At the cut-off date of February 1st, 2015, 24 patients were still on treatment with first-line EGFR-TKI, while the remaining 288 had progressed or died. Among these, 274 patients (95.1%) received a second-line treatment including an active systemic therapy, a local one or best supportive care alone. In detail, 163 (59.4) patients received a second-line systemic therapy: platinum-doublets were the preferred chemotherapy regimen (108 patients, 66.2%), and pemetrexed in combination with cisplatin or carboplatin was the favorite choice (97 patients, 59.5%) while in one case only a platinum-triplet was administered. Single-agent chemotherapy was administered to 35 patients (21.5%). In 15 cases (9.2%) a shift to a different EGFR-TKI was prescribed and afatinib was the preferred choice. Finally, 2 patients continued with gefitinib added to a platinum-doublet chemotherapy, within a clinical trial (however these data was not specifically recorded within the study database). A total of 103 patients were considered for best supportive care

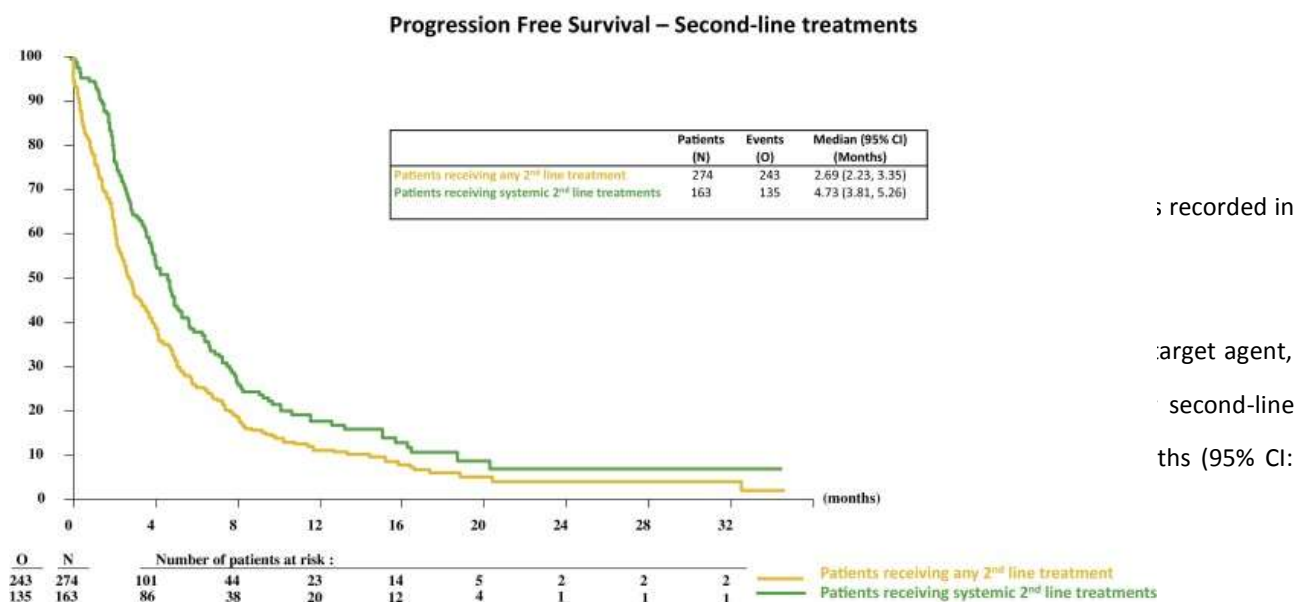


Fig. 2.

Progression Free Survival – comparison among patients receiving any second-line treatment (considering as “any second-line treatment”: chemotherapy and/or target therapy, local treatments and best supportive care) and patients receiving second-line systemic treatments (considering as “second-line systemic treatment”: chemotherapy and/or target therapy).

In the 97 patients receiving platinum/pemetrexed combination, ORR was 28.9% (95% CI: 19.85–37.88), with a median PFS of 5.2 months (95% CI: 4.07, 6.77). Namely, in 54 patients who received cisplatin/pemetrexed regimen, ORR was 33.3% (95% CI: 20.76–45.91) with a median PFS of 5.8 months (95% CI: 4.21–7.72), while in 43 patients who underwent carboplatin/pemetrexed treatment, ORR was 23.3% (95% CI: 10.63–35.88) with a median PFS of 2 months (95% CI: 1.22–2.92).

Single-agent chemotherapy was administered to 35 patients, pemetrexed (n = 14) and gemcitabine (n = 13) were largely used, and produced an ORR of 0% and 15.4% (95% CI: 0–0.35), with a median PFS of 2.6 (95% CI: 2.07–3.68) and 3.7 (95% CI: 1.97–5.42) months, respectively.

Subpopulation with brain metastasis had a shorter PFS considering both first- and second-line treatments: median PFS 8.97 (CI: 7.13, 11.07) versus 9.82 months (CI: 8.61, 11.50) for first-line treatment, in patients with brain metastases and those without, respectively; and median PFS of 2.56 (CI: 1.05, 3.98) versus 2.79 months (CI: 2.23, 3.52) for second line treatments, respectively.

Finally in those 15 patients who underwent a shift to another EGFR-TKI the ORR was 13.3% (95% CI: 0–30.54) with median PFS equal to 6.4 (95% CI: 1.84–8.05) months. A concomitant ALK translocation was reported in two patients who received Crizotinib.

Second-line treatments were overall well tolerated, with grade 3–4 hematological and non-hematological toxicities reported in 13 (9%) and 9 (6.3%) out of the 144 patients treated with chemotherapy, respectively. Among chemotherapy regimens, patients receiving platinum-doublets had more grade 3–4 than those receiving single-agent chemotherapy: 11 (10.1%) versus 2 (5.7%) and 8 (7.3%) versus 1 (2.9%), for hematological and non-hematological toxicities, respectively. In the 17 patients receiving second-line targeted agents grade 3–4 non-hematological toxicity was reported in 4 cases (23.5%).

Finally, on 274 eligible patient for any second-line treatment, in 56.9% of them (n = 156) PS at the end of second-line treatment was improved or maintained, it worsened in 1.2% of cases (n = 3), while for 115 patients PS informations during different treatments were incomplete.

As first-line treatment, the majority of patients received gefitinib (288 patients, 92.3%), only 24 received erlotinib (7.7%). In 81.7% of patients (n = 255) PS at the end of EGFR-TKI was improved or maintained, whereas PS worsened in 7% of cases (n = 22); post first-line treatment PS was missing in 35 (11.2%) cases.

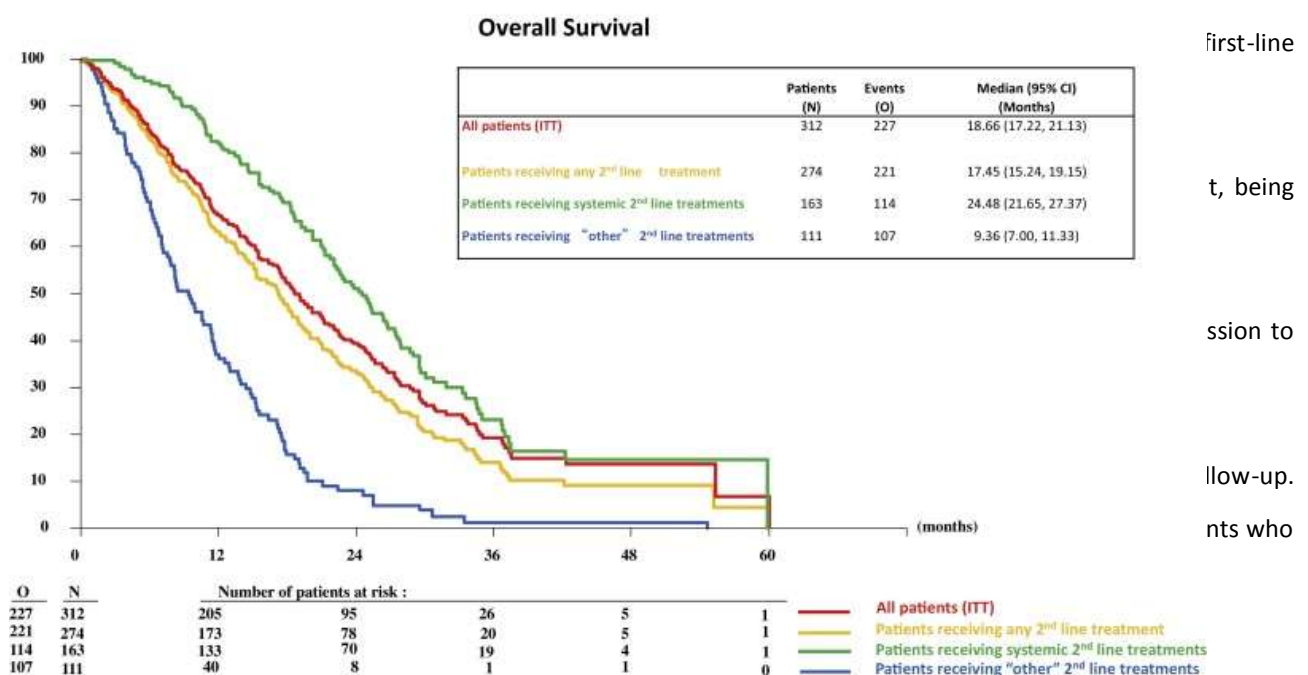


Fig. 3.

Comparison of Overall Survival among all patients, patients receiving any second-line treatment (considering as “any second-line treatment”: chemotherapy and/or target therapy, local treatments and best supportive care), patients receiving systemic second-line treatments (considering as “second-line systemic treatment”: chemotherapy and/or target therapy) and patients receiving “other” second-line treatments (considering as “other” second-line treatments: local treatments only or best supportive care).

Second-line treatments and efficacy data of main subgroups are described in Table 3.

Table 3.

Second-line treatments and efficacy data of main subgroups.

Treatments	Patients (N)	ORR (%)	DCR (%)	Median PFS (95% CI) (Months)	Median OS (95% CI) (Months)	Median OS of second-line (95% CI) (Months)
Chemotherapy	144	22.22	56.25	4.37 (3.65, 5.06)	24.21 (21.09, 26.64)	11.66 (8.84, 13.34)
Cisplatin + pemetrexed	54	33.33	68.52	5.78 (4.21, 7.72)	27.47 (24.84, 33.58)	16.62 (11.66, 19.45)
Carboplatin + pemetrexed	43	23.26	60.47	2.04 (1.22, 2.92)	23.72 (17.28, 29.54)	7.79 (4.83, 13.77)
Pemetrexed	14	0.00	35.71	2.56 (2.07, 3.68)	21.73 (13.90, 29.57)	4.40 (3.19, 10.74)
Gemcitabine	13	15.38	46.15	3.68 (1.97, 5.42)	19.19 (12.32, 22.51)	8.44 (3.94, 11.86)
Targeted Agent	17	11.76	52.94	6.41 (1.84, 8.05)	29.54 (14.49, N)	16.95 (3.98, 23.66)
Gefitinib	3	33.33	100.00	6.54 (6.41, N)	Not reached	Not reached
Erlotinib	5	0.00	40.00	4.37 (0.46, N)	20.21 (8.57, N)	4.70 (0.46, 17.71)

Treatments	Patients (N)	ORR (%)	DCR (%)	Median PFS (95% CI) (Months)	Median OS (95% CI) (Months)	Median OS of second-line (95% CI) (Months)
Afatinib	7	14.29	42.86	5.36 (1.51, N)	30.18 (11.27, N)	16.95 (3.12, 23.66)
Crizotinib	2	0.00	50.00	3.98 (N, N)	Not reached	3.98 (N, N)
Other	111	0	1.80	1.05 (0.79, 1.41)	9.36 (7.00, 11.33)	1.05 (0.82, 1.74)
Radiotherapy	6	–	16.67	1.64 (0.23, 5.03)	14.26 (11.33, N)	3.32 (1.05, 7.85)
Best supportive care	103	–	0.97	1.02 (0.72, 1.41)	8.15 (6.80, 10.58)	1.02 (0.72, 1.45)
All systemic second-line treatments	163	20.86	56.44	4.73 (3.81, 5.26)	24.48 (21.65, 27.37)	11.86 (8.94, 14.42)
Patients receiving any second-line treatment	274	12.41	34.31	2.69 (2.23, 3.35)	17.45 (15.24, 19.15)	4.40 (3.58, 5.98)

ORR: Objective Response Rate; DCR: Disease Control Rate; PFS: Progression Free Survival; OS: overall survival

4. Discussion and conclusions

To best of our knowledge, BE-POSITIVE study is the largest observational non-interventional study evaluating treatments beyond TKIs PD in Caucasians EGFR mutated patients. At the cut-off date, 163 patients (59.4%), out of 274 who were eligible for second-line treatment, received a chemotherapy as the preferred option and 40.5% of patients did not receive any further systemic therapy. This last data is in line with the RIGHT-3 study in which 39.1% of patients did not access a second line treatment [23]. However, the RIGHT-3 was an observational trial, which aimed to evaluate concordance between Italian lung cancer guidelines and Italian clinical practice and enrolled patients not selected for histology and EGFR mutational status. On the other hand, the percentage of patients receiving second-line treatment in our series was slightly lower compared to phase III trials of first-line EGFR-TKI versus chemotherapy: in those studies, that proportion ranged from 63.4% to 88.1% [7], [8], [9], [10] and [11]. These data underline that patients enrolled in clinical trials do not necessarily reflect the “real life population”. In our study elderly patients (aged ≥ 70 years) were 41.7% of the overall population and patients with PS ≥ 2 were 13.7%. These special patients’ populations, if not EGFR mutated, have a lower chance to be treated even with a first-line chemotherapy. In fact, considering patients aged ≥ 70 years, although prospective trials support the use of first-line carboplatin-based doublets in fit elderly patients and single-agent treatment for less fit ones, they evidenced higher rates of adverse events (AEs) during chemotherapy: adjusted rate ratios 1.70 (95% CI 1.19–2.43) for 65- to 74-year-old patients, and 1.34 (95% CI 0.90-2.00) for patients aged 75 or older compared with patients younger than 55 years [24]. A Comprehensive Geriatric Assessment (CGA) was demonstrated to predict the risk of chemotherapy toxicity, but it is not systematically used in clinical practice because it is a time and man-power consuming process, confirming the risk of under-treatment in these patients [25]. Taking into account also PS, Inoue et al. enrolled patients 20–74 years-old with ECOG PS 3–4, 75–79 years-old with PS 2–4, and 80 years-old with PS 1–4 who had advanced NSCLC harbouring EGFR mutations. The ORR was 66%, DCR (disease control rate) was 90% and PS improvement rate was 79% ($p < 0.00005$); particularly, 68% of the 22 patients improved from \geq PS 3 at baseline to \leq PS 1 [26]. Considering these acquisitions, it is of paramount importance to define the EGFR status also in these categories of patients, mainly if clinical characteristics relate with the presence of an activating EGFR mutation, in order to receive a possible highly active and well tolerated treatment, even in frail patients.

Platinum-based regimens were administered to 111 (68% out of 163 who received second-line systemic therapy) patients and 97 (59.5%) received platinum/pemetrexed combination. The percentage of patients receiving second-line platinum-based treatments was in line with those showed by phase III trials, which ranged from 42.6% to 76.3% [7], [8], [9], [10] and [11]. In our study patients receiving platinum-pemetrexed regimens reported an ORR of 28.9% with a median PFS of 5.2 months, and a median OS of 26.3 months. Our results are similar to those reported by Tseng et al., who showed data concerning the combination of platinum/pemetrexed administered as second-line treatment in 61 patients receiving first-line EGFR-TKI and those on 44 patients receiving the regimen as first-line therapy, retrospectively collected and compared. ORR of second-line versus first-line platinum/pemetrexed therapy was 24.6% and 38.6%, respectively. The median PFS was 6.1 months in both groups with a median OS of 34.4 and 32.2 months, respectively [27]. In the present study, 54 patients received cisplatin/pemetrexed regimen reporting an ORR of 33.3%, with a median PFS of 5.8 months. These data are superimposable to those showed by the IMPRESS trial, in which

EGFR-mutated patients progressed to first-line gefitinib, when treated with cisplatin/pemetrexed regimen reported an ORR of 34% with a median PFS of 5.4 months [28]. The cisplatin/pemetrexed regimen scored better, in terms of ORR (33.3% versus 23.3%) and median PFS (5.8 versus 2.0 months), than carboplatin/pemetrexed combination. Considering that our study is predominantly a retrospective analysis, we can assume that these differences should be due to the younger age (median age: 59.2 versus 69.3 years-old, respectively), and to a better PS (PS = 0: 61.1% vs 30%; PS 1–2: 38.9% versus 70%, respectively) of patients analyzed. Finally, in LUX-Lung 3 trial, first-line cisplatin/pemetrexed regimen showed a surprising lower ORR (23% by independent assessment), but a longer median PFS of 6.9 months [3]. These slightly discordant data could be attributed to the fact that treatment was administered in different lines of therapy. Overall, they confirmed platinum/pemetrexed as the preferred approach for EGFR-mutated lung adenocarcinoma patients progressing after first-line EGFR-TKI.

The characteristics of patients enrolled in the BE-POSITIVE study confirmed the historical literature data: most of patients were females, never smokers and with adenocarcinoma histology [14]. The subgroup of current smokers (n = 7) (>30 pack/year), all treated with gefitinib, when compared to the overall gefitinib population, had a worse median PFS (4.7 versus 9.4 months) and median OS (15.4 versus 17.8 months) as showed by literature data [29], [30], [31] and [32]. Finally, uncommon EGFR mutations were heterogeneous in prevalence (9.3% of the overall population), confirming the report of the ERMETIC study in which, on 1.047 samples, rare mutations were detected in 10% of patients [33]. This subgroup of patients will be specifically described in a separate publication.

Safety data demonstrated that both EGFR-TKIs were well tolerated or had manageable toxicities.

Median duration of treatment was about 9 months for both gefitinib and erlotinib, similar to the 8 months reported by the IFUM study [14]. Patients receiving gefitinib reported an ORR of 50%, which was lower than that showed in the IFUM study (ORR 69.8% based on investigator assessment), but exactly in line with the ORR of 50% showed by secondary central review in the same study [14].

In our cohort, palliative RT was administered in 23.4% of patients during EGFR-TKI, due to oligoprogression of disease. All these patients continued on treatment beyond progression with EGFR-TKI until a clear systemic progression or loss of the clinical benefit. Unfortunately, DCR after first oligo-progression was not planned to be recorded at the time of study design. This strategy has not been validated in a randomized trial, but it was prospectively assessed in the ASPIRATION trial, in which the continuation of erlotinib beyond formal PD according to RECIST criteria led to a prolonged administration of erlotinib, until further progression: particularly, of the 207 intent-to-treat patients (62.3% female; median age, 60.8 [range, 28–89] years), 176 had a PFS1 event (171 progression and 5 deaths); of these, 78 discontinued and 93 continued erlotinib therapy following progression. Median PFS1 and PFS2 in the 93 continuing patients were 11.0 (95% CI, 9.2–11.1) and 14.1 (95% CI, 12.2–15.9) months, respectively [34], [35] and [36].

In conclusion, BE-POSITIVE is the first large study on “*real-life*” Caucasian patients with EGFR-mutated NSCLC describing disease characteristics and clinical behaviours throughout first- and second-line approaches, thus providing an overview of the less well characterized setting of second-line therapies. There is still a huge need of improving

treatment options for advanced NSCLC EGFR-mutated patients at the time when EGFR resistance, other than the onset of T790M, develops.

Conflict of interest statement

Alessandro Morabito declared a consultancy role for AstraZeneca, Roche, Boehringer Ingelheim.

Diego Cortinovis declared a consultancy role for Boehringer Ingelheim, boards' participation for Novartis, Roche, Eli Lilly and speaker's fee from Boehringer Ingelheim and Pfizer.

Emilio Bria declared a consultancy role for Celgene, boards' participation for Novartis, Astra-Zeneca, Pierre-Fabre, and speaker's fee from Pfizer and MSD.

Antonio Rossi declared a role as Speaker Bureau for Roche, Boehringer Ingelheim, advisory boards' participation for Eli Lilly, AstraZeneca.

Silvia Novello declared a role as Speaker Bureau for Roche, Boehringer Ingelheim, Eli Lilly, AstraZeneca, MSD.

All other authors have no conflict of interest to declare.

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Appendix A

Table A1.

Characteristics of second-line approaches.

Approaches	No.pts
Chemotherapy	144
Cisplatin + pemetrexed	54
Carboplatin + pemetrexed	43
Cisplatin + gemcitabine	5

Approaches	No.pts
Carboplatin + gemcitabine	3
Carboplatin + paclitaxel	3
Pemetrexed	14
Gemcitabine	13
Docetaxel	3
Paclitaxel	1
Vinorelbine	2
Carboplatin	2
Capecitabine + oxaliplatin + bevacizumab	1
Targeted Agent	17
Gefitinib	3
Erlotinib	5
Afatinib	7
Crizotinib	2
Chemotherapy + EGFR-TKI	2
Cisplatin + pemetrexed + gefitinib	2
Other	111
Radiotherapy	6
Adrenalectomy	1
Intratecal methotrexate	1
Best supportive care	103

Approaches	No.pts
All systemic second line treatments	163
All	274

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