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Clinical Trial Results

First-Line Osimertinib in Patients with *EGFR*-Mutant Advanced Non-Small Cell Lung Cancer: Outcome and Safety in the Real World: FLOWER Study

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Abstract

Background: Osimertinib became the standard treatment for patients with untreated *EGFR*-mutant advanced non-small cell lung cancer (aNSCLC) following results reported in the phase III randomized FLAURA trial. Because of strict exclusion criteria, patient populations included in pivotal trials are only partially representative of real-world patients.

Methods: We designed an observational, prospective, multicenter study enrolling patients with *EGFR*-mutant aNSCLC receiving first-line osimertinib to evaluate effectiveness, safety, and progression patterns in the real-world.

Results: At data cutoff, 126 White patients from nine oncology centers were included. At diagnosis, 16 patients (12.7%) had a performance status (PS) ≥2 and 38 (30.2%) had brain metastases. Overall response rate (ORR) was 73%, disease control rate (DCR) 96.0%. After a median follow-up of 12.3 months, median time to treatment discontinuation (mTTD) was 25.3 months, median progression-free-survival (mPFS) was 18.9 months and median overall survival (mOS) was not reached (NR). One hundred and ten patients (87%) experienced adverse events (AEs), 42 (33%) of grade 3–4, with venous thromboembolism (VTE) as the most common (n = 10, 7.9%). No difference in rates of VTE was reported according to age, PS, comorbidity, and tumor load. We observed longer mTTD in patients without symptoms (NR vs. 18.8 months) and with fewer than three metastatic sites at diagnosis (NR vs. 21.4 months). Patients without brain metastases experienced longer mPFS (NR vs. 13.3 months). No difference in survival outcome was observed according to age, comorbidity, and type of *EGFR* mutation. Isolated progression and progression in fewer than three sites were associated with longer time to treatment discontinuation (TTD).

Conclusion: Osimertinib confirmed effectiveness and safety in the real world, although thromboembolism was more frequent than previously reported.

Key words: osimertinib; real-world study; epidermal growth factor receptor; non-small cell lung cancer.

Lessons Learned

- Osimertinib has confirmed effectiveness in this real-world population of patients with *EGFR*-mutant advanced non-small cell lung cancer.
- Thromboembolic events occur more frequently than previously reported, suggesting a thrombotic diathesis that requires further investigation.
- Patients with at least three metastatic sites, brain metastases, and symptoms at diagnosis seem to have a worse prognosis.

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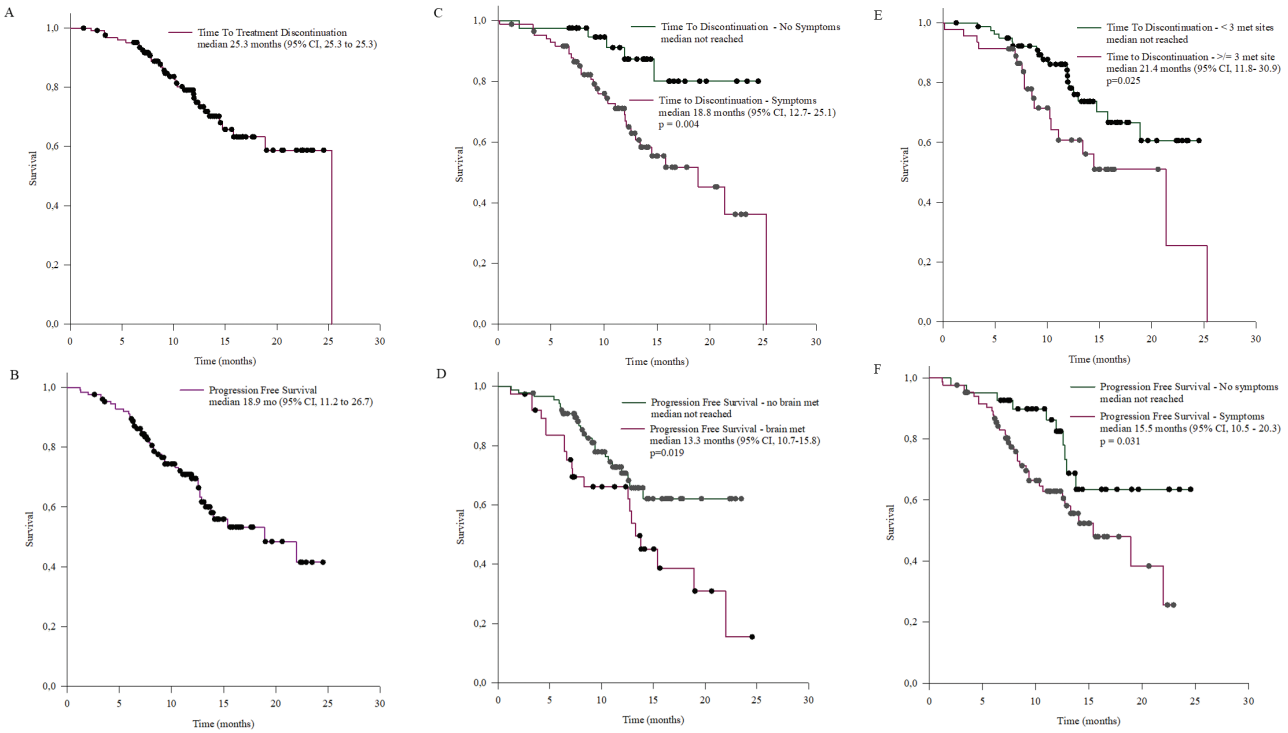

Figure 1. Survival curves of patients with *EGFR*-mutant non-small cell lung cancer receiving first-line osimertinib. Kaplan-Meier survival curves representing the following: median time to treatment discontinuation (mTTD) **(A)** and median progression-free survival (mPFS) **(B)** in patients receiving front-line treatment with third-generation epidermal growth factor receptor-tyrosine kinase inhibitors, osimertinib; mTTD in patients with or without symptoms at diagnosis **(C)**; mPFS in patients with or without brain metastases at diagnosis **(D)**; mTTD in patients with less than three or at least three metastatic sites **(E)**; and finally mPFS in patients with and without symptoms at diagnosis **(F)**.Abbreviation: CI, confidence interval.

Discussion

FLOWER (First-Line Osimertinib in the real-World: an intER-regional prospective study) is an observational prospective multicenter study aiming at describing outcome, safety, progression pattern, and clinical management of untreated patients with *EGFR*-mutant aNSCLC receiving first-line osimertinib in the real world.

We included patients with poor PS, comorbidities, rare *EGFR* mutations, and active brain metastases, who were excluded from the pivotal, phase III FLAURA trial.[1,2] Indeed, randomized controlled trials (RCTs), the gold standard for assessing efficacy and safety of new drugs, often lack such specific subpopulations due to strict exclusion criteria.

Despite difference in baseline clinical characteristics, outcomes were similar to published data, thus adding consistency to osimertinib efficacy.[1] In particular, no difference in progression-free survival (PFS), TTD, and overall survival (OS) were noted in elderly patients and patients with comorbidity and less common *EGFR* mutations, highlighted as osimertinib seems to be effective also in these subpopulations. However, we reported a worse treatment outcome for patients with brain metastases, presence of symptoms, and at least three metastatic sites at diagnosis, suggesting tumor load as a negative prognostic factor (Figure 1).

TTD appears to be a more suitable endpoint to evaluate treatment outcomes in pragmatic real-world trials on tyrosine kinase inhibitors (TKIs), in which treatment beyond progression is a common practice.[3] In our study, TTD was longer (25.3 months) than the postprogression outcomes analysis of FLAURA trial (20.8 months), probably due to our unselected population comprising patients unfit for further treatment and a different management of oligoprogressive disease. Moreover, better TTD was associated with fewer than three progressing sites (p =.050) and isolated progression (p =.018) compared with oligo- or systemic progression. No difference in PFS was reported in these subgroups.

Regarding safety, most common any grade AEs were diarrhea (n = 49, 38.9%), skin rash (n = 42, 33.3%), and paronychia (n = 33, 26.2%), whereas venous thromboembolism was the most frequent severe AE (n = 10, 7.9%). In the FLAURA trial grade 3–4 thromboembolic events were more frequent in the osimertinib arm compared with the control arm (3% vs. 0.7%), while in the AURA 3 trial, pulmonary embolism was the most common serious AE with osimertinib. These data suggest a thrombotic diathesis in patients receiving osimertinib and needs further investigation.[1,4]

Finally, we described the diagnostic-therapeutic pathway of patients treated in clinical practice, providing information that may be challenging to assess using only data from RCTs. This is an essential element of evidence-based medicine and could help clinician in decision making.

Author disclosures and references available online.

Trial Information	
Disease	Lung cancer - NSCLC - *EGFR*-mutant
Stage of Disease/ Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study	Observational real-world single-arm study
Primary Endpoints	Time to treatment discontinuation, toxicity
Secondary Endpoints	Progression-free survival, overall survival, overall response rate, disease control rate, assessment of progression patterns to osimertinib, correlation of baseline clinical features with survival
Investigator's Analysis	Active and should be pursued further

Additional Details of Endpoints or Study Design

Study Design and Patients

FLOWER is a real-world, prospective, observational study enrolling patients referred to nine Italian oncology centers. Main inclusion criteria were the following: age >18 years, histological and/or cytological confirmed diagnosis of NSCLC, presence of one or more epidermal growth factor receptor (*EGFR*) mutations in exon 18–21, locally advanced, recurrent or metastatic disease (stage IIIB and IV according to 8th edition of the TNM Classification of Malignant Tumors) and eligible to receive first-line treatment with the third-generation *EGFR* TKI, osimertinib. Patients who received the study drug in clinical trials were excluded. Patients were included before starting the study drug. This study was approved by the ethical committees of each participating center and conducted in accordance with Good Clinical Practice guidelines and the Helsinki declaration. All the participants signed the specific Informed Consent Form.

Clinical data collected at baseline included the following: gender, age, smoking status, Eastern Cooperative Oncology Group PS, Charlson Comorbidity Index, tumor histology, type of *EGFR* mutation, previous treatments, stage at diagnosis according to the 8th edition of the TNM Classification of Malignant Tumors, baseline metastatic sites, presence of disease-related symptoms. During treatment, we registered radiological assessment (according to RECIST version 1.1) and data about treatment-related AEs and their grade, according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, and their relationship, with osimertinib therapy. At the time of disease progression, data recorded were the following: type and number of metastatic sites and disease-related symptoms, subsequent systemic, or locoregional treatment, rebiopsy, and date of treatment discontinuation. At data cut-off we registered patients' status, date of death or last follow-up. Radiological tumor assessment was performed according to the clinical practice of each oncological center. Disease progression was classified in three different patterns: solitary progression (appearance or growth of one lesion), oligoprogression (progression or appearance of up to three lesions in two organs), and systemic progression (progression or appearance of more than three lesions). Treatment beyond progression was allowed as long as a clinical benefit loss, as judged by the investigators.

Endpoints

Primary endpoints were evaluation of (a) mTTD, measured from the osimertinib start to discontinuation for any cause, (b) rate of treatment-related AEs, and (c) rate of dose reduction and temporary or definitive treatment interruption due to AEs.

Secondary endpoints included (a) the assessment of mOS, measured between the osimertinib start and death for any cause; mPFS measured as the time between osimertinib start and the evidence of progression or death; ORR, and DCR; (b) the assessment of progression patterns to osimertinib, in terms of number and localization of metastatic sites, new lesions, and progression related symptoms; and (c) the correlation of baseline clinical-pathological features with survival. We also explored the diagnostic-therapeutic pathway of patients describing (a) the time frame between diagnostic biopsy, histologic report (including *EGFR* mutation test report) and treatment start; (b) the proportion of patients underwent locoregional treatment, and (c) type and frequency of rebiopsy performed at progression.

Molecular Testing

EGFR mutations in exons 18–21 were tested at diagnosis through liquid or tissue biopsy. For analyses on tissue sample, tumor DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor slices through QIAamp DNA FFPE kit (Qiagen, Hilden, Germany); DNA sequencing was carried out with Sanger sequencing, pyrosequencing, polymerase chain reaction (PCR)–based methods (easy PGX ready *EGFR* kit, Diatech Pharmacogenetics, Jesi, Italy; cobas *EGFR* Mutation Test v2, Roche, Basel, Switzerland; *EGFR* mutation analysis kit EntroGen, EntroGen, Woodland Hills, CA; Scorpion-ARMS *EGFR* Plasma RGQ PCR Kit, Qiagen, Hilden, Germany), mass spectrometry-based methods (Sequenom MassARRAY, Diatech Pharmacogenetics, Jesi, Italy), or next generation sequencing. For liquid biopsy, cell-free (cf-) DNA was isolated from 2 mL of plasma using the cobas cf-DNA Sample Preparation kit (Roche, Basel, Switzerland) and analyzed with the techniques described above.

Statistical Analysis

Statistical analysis was performed through Sigma-Plot (Systat Software, San Jose, CA) software. mTTD, mPFS, and mOS were estimated using the Kaplan-Meier method. The χ^2, Mann-Whitney, or Fisher exact test and multiple logistic regression were used for correlation analysis. The log-rank test and Cox proportional hazard model were applied to identify the impact of each clinical-pathological features on outcome.

Drug Information	
Generic Name	Osimertinib
Drug Type	Small molecule
Drug Class	*EGFR*
Dose	80 mg
Route	p.o.
Schedule of Administration	All patients received osimertinib at the recommended dose of 80 mg, orally, once a day. Dosing interruptions or reductions required, based on individual tolerability, were managed according to clinical practice in compliance with label indications.

Patient Characteristics	
Number of Patients, Male	45
Number of Patients, Female	81
Stage at Diagnosis	IIIB/IIIC: 6 (4.8) IVA: 30 (23.8) IVB: 90 (71.4)
Age	Median (range): 68 (30–88) years
Number of Prior Systemic Therapies	0
Other	From June 2018 through September 2020, a total of 126 patients from nine oncology centers were included. All cases received at least one dose of osimertinib. All patients have a follow-up of at least 6 months. Baseline patients' characteristics are described in Table 1. All patients were White; median age was 68 years (range 30–88 years). At diagnosis, 12.7% of patients (n = 16) had a PS ≥ 2 and 5.7% (n = 7) harbored rare or complex *EGFR* mutations. At baseline radiologic assessment, 30.2% of patients (n = 38) had brain metastases.
Cancer Types or Histologic Subtypes	Adenocarcinoma, 120 Squamous cell carcinoma, 3 Adenosquamous carcinoma, 2 Unknown, 1

Primary Assessment Method: Effectiveness	
Number of Patients Screened	126
Number of Patients Enrolled	126
Number of Patients Evaluable for Toxicity	126
Number of Patients Evaluated for Efficacy	126
Evaluation Method	RECIST 1.1
Response Assessment CR	n = 0 (0%)
Response Assessment PR	n = 92 (73%)
Response Assessment SD	n = 29 (23%)
Response Assessment PD	n = 5 (4%)
(Median) Duration Assessments PFS	18.9 Months, confidence interval (CI): 95% CI, 11.2–26.7

Outcome Notes

ORR was 73% (95% CI, 65.5–80.8) and DCR 96% (95% CI, 92.6–99.4). After a median follow-up of 12.3 months from osimertinib start, mTTD was 25.3 months (95% CI, 25.3–25.3) and mPFS was 18.9 months (95% CI, 11.2–26.7) (Fig. 1A, 1B). mOS was not reached at the time of data cut-off (81% of censored subjects). We observed a statistically significant longer TTD in patients without symptoms at diagnosis (median not reached vs. 18.8 months; p =.004) and in patients with less than three metastatic sites at diagnosis (median not reached vs. 21.4 months; p =.025) (Fig. 1C–1E). Multivariate analysis for TTD confirmed the correlation with the absence of symptoms (hazard ratio [HR], 3.035; 95% CI, 1.126–8.178; p =.028) and suggested a trend toward association for the number of metastatic sites (<3 vs. ≥3 metastatic sites; Table 2), although without statistical significance. Absence of brain metastases at diagnosis was correlated with longer PFS (median not reached vs. 13.3 months; Fig. 1D) in univariate (p =.019) and multivariate analysis (HR, 2.382; 95% CI, 1.061–5.344; p =.035; Table 2). Moreover, in patients without symptoms at diagnosis, we observed a prolonged PFS (median not reached vs. 15.5 months; p =.031; Fig. 1F) and longer OS (median not reached vs. 21.3 months; p =.022) with a trend to significance in multivariate analysis for OS (p =.059; HR, 3.480; 95% CI, 0.955–12.678). To explore the impact of PFS and TTD on OS, we categorized patients on the basis of PFS and TTD value (9 months cut-off). At univariate analysis, prolonged OS was reported in patients with a PFS (p <.001) and TTD (p <.001) longer than 9 months. Multivariate analysis confirmed that TTD of 9 months or higher was significantly associated with better OS (p =.008; HR, 0.145; 95% CI, 0.035–0.599; Table 3.)

Secondary Assessment Method: Progression Pattern	
Number of Patients Screened	126
Number of Patients Enrolled	126
Number of Patients Evaluable for toxicity	126
Number of Patients Evaluated for Efficacy	126
Evaluation Method	RECIST 1.1

Outcome Notes: Progression pattern

Data on progression pattern are summarized in Table 4. Among patients experiencing progressive disease (PD; *n* = 44, 34.9%), median number of progressing sites was two (range 1–7) and 70.5% of patients (*n* = 31) progressed in less than thee sites. The most frequent progressing sites were lung (*n* = 28, 63.6%), bone (*n* = 15, 34.1%) and brain (*n* = 9, 20.5%). At least one new progressing site was registered in 18 cases (40.9%), median number was one (range 1–4). An isolated progression occurred in 8 cases (18.2%), oligoprogression in 9 patients (20.5%), and systemic progression in 24 cases (54.5%). Progression patterns are depicted in Figure 2. A longer TTD was shown in patients with isolated progression compared with oligo- or systemic progression (not reached vs. 10.4 months; 95% CI, 8.2–12.6; *p* =.018) and in patients with fewer than three progressing sites (12.9 months; 95% CI, 10.7–15.3, vs. 8.5 months; 95% CI, 4.4–12.7; *p* =.050). Locoregional nodes progression and progression in fewer than three new sites appeared to be correlated with better survival outcomes (Table 4).

Primary Assessment Method: Real-World Diagnostic-Therapeutic Pathway	
Number of Patients Screened	126
Number of Patients Enrolled	126
Number of Patients Evaluable for Toxicity	126
Number of Patients Evaluated for Efficacy	126
Evaluation Method	Description

Outcome Notes

Time frame between diagnostic procedure, histological and molecular reports and treatment start were summarized in Table 5. In patients without recurrent disease (*n* = 107, 84.9%), median time from biopsy to pathologic report was 7.0 days (range 2–55), median time from pathologic report to *EGFR* mutation status report was 8 days (range 3–56) and median time to osimertinib start from *EGFR* mutation status report was 17 days (range –1 to 301). Median time to treatment start was significantly longer when osimertinib access was off-label or in class C not negotiated (C-NN class), compared with hospital class (H class)/AIFA register prescription (24 vs. 12 days; *p* <.001). Among patients experiencing PD (*n* = 44), 21 cases (47.7%) underwent a rebiopsy at progression. Tissue rebiopsy was performed in 14 cases (66.7%), liquid in others (*n* = 6, 28.6%); one case underwent both tissue and liquid biopsy. Molecular analysis was performed in 13 samples (61.9%); druggable resistance mechanisms included the following: *MET* amplification (amp) (*n* = 4), *MET* amp/*EGFR* amp (*n* = 1), *EGFR* amp (*n* = 1), *HER2* amp (*n* = 1); in four cases the analysis was ongoing at the time of data cut-off. Thirty-nine (31%) patients received palliative locoregional treatment. Among them, the first local treatment was received within a month from osimertinib start in 21 (53.8%). Median time to first treatment for the other 16 cases was 8.5 months (range 2.1–17.7). Brain radiotherapy was performed in 15.1% of patients enrolled (*n* = 19). Further details on locoregional treatment are summarized in Table 6.

Adverse Events

All AEs are summarized in Table 7. AEs of any grade were reported in 87.3% of patients (*n* = 110); the most frequently experienced were diarrhea (*n* = 49, 38.9%), skin rash (*n* = 42, 33.3%), and paronychia (*n* = 33, 26.2%). Grade 3 or higher AEs occurred in 33.0% of cases (*n* = 42); the most common were venous thromboembolic events (*n* = 10, 7.9%). Moreover, three patients (2.4%) experienced an arterial thromboembolism, two of them (1.6%) of grade 3 or higher. No statistically significant difference in the rate of venous thromboembolism was found in elderly patients, those with poor PS, comorbidity, or at least three metastatic sites, although a trend toward a higher rate of events was reported in patients younger than 65 years (Table 8). Fatal AEs occurred in two patients (1.6%): fungal pneumonia and cardiac heart failure. The second one was considered possibly related with the drug by investigators. Temporary interruption for AEs was registered in 25 cases (19.8%), most frequently because of platelet count decrease (4.8%) and diarrhea (3.2%). A dose reduction due to AEs occurred in 11 (8.7%) patients. Treatment was permanently discontinued for toxicities in nine cases (7.1%). Most common causes of discontinuation were interstitial lung disease/pneumonitis (*n* = 3, 2.4%), arterial thromboembolism (*n* = 2, 1.6%), and venous thromboembolism (*n* = 1, 0.8%). Further details on AEs and management are provided in the Table 9.

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's Assessment	Active and should be pursued further

In patients with *EGFR*-mutant advanced non-small cell lung cancer (aNSCLC), treatment with epidermal growth factor receptor (*EGFR*)-tyrosine kinase inhibitors (TKIs) improved outcome compared with platinum-based chemotherapy.[1,5-11] Osimertinib, an irreversible, third-generation *EGFR* TKI, demonstrated a clinically meaningful improvement in median progression-free survival (mPFS) compared with first-generation *EGFR*-TKIs, erlotinib or gefitinib, (mPFS, 18.9 months vs. 10.2; hazard ratio [HR], 0.46; 95% confidence interval [CI], 0.37–0.57; p <.001) and a similar safety profile with lower rates of serious adverse events (AEs), in the phase III randomized FLAURA trial.[1] Moreover, high activity in the central nervous system (CNS) leading to improved CNS-progressive-free survival (PFS) was registered.[12,13] These results, along with the overall survival (OS) benefit reported despite crossover (median OS, 38.6 months vs. 31.8; HR, 0.80; 95% CI, 0.64–1.00), made osimertinib the best treatment option for patients with untreated *EGFR*-mutant aNSCLC.[2]

Randomized controlled trials (RCTs) remain the gold standard for assessing efficacy and safety of new drugs. However, specific subpopulations such as elderly patients, and patients with poor performance status (PS), active brain metastases, and comorbidities are frequently excluded. In addition, treatment sequencing and management of oligoprogression are hardly assessable in pivotal trials, because of protocol limitations.

In this scenario, real-world studies can provide data from patients treated in clinical practice.[14,15] Indeed, it has been estimated that only 2%–4% of patients with cancer receive treatment within RCTs, thus raising the issue of the representativeness for a real-world population and the external validity of results.[16,17] Real-world data have become useful tools for different stakeholders (patients, physicians, regulatory agencies) to assess unique insights in routine oncology practice in the postmarketing setting.[15]

FLOWER is a real-world, prospective, observational study enrolling patients referred to nine Italian oncology centers (Table 10). To the best of our knowledge, FLOWER is the first real-world prospective study investigating effectiveness and safety of first-line osimertinib. Compared with the FLAURA trial population, we also enrolled patients with poor PS (≥2), older patients (median age 68 vs. 64 years), patients with comorbidities, and patients with uncommon *EGFR* mutations. Moreover, the percentage of patients with brain metastases at baseline was higher in our study (30.2% vs. 19% in FLAURA trial), possibly because of the inclusion of patients with unstable and symptomatic brain metastases, excluded from the pivotal trial.[1]

Despite difference in baseline characteristics, PFS, overall response rate, and disease control rate are in line with published data.[1,18] In particular no statistically significant difference in PFS, time to discontinuation (TTD), and OS were noted in elderly patients, patients with comorbidities, and patients with less common *EGFR* mutations. In contrast, patients with brain metastases, symptoms, and at least three metastatic sites at diagnosis tend to have worse outcomes, suggesting tumor load as a relevant negative prognostic factor (Table 2).

Of note, TTD in the overall population was slightly longer (25.3 months) than previously reported in the postprogression outcomes analysis of FLAURA trial (20.8 months). This gap could be explained by the inclusion in our study of patients with poor PS, frequently considered unfit for further standard treatment at progression (i.e., chemotherapy), and the different management of oligoprogression outside RCTs.[19]

TTD is under exploration as a pragmatic real-world endpoint to assess effectiveness of anticancer therapy in NSCLC because it is easily extracted from electronic health care records and reflects the common practice to continue treatment beyond RECIST progression, justified by the biology of oncogene addicted tumors, in which oligoprogression frequently occurs, and the favorable safety profile of targeted therapies.[3,20,21] In our study, 38% of patients experienced an isolated or oligoprogression and 41% received locoregional treatments during osimertinib therapy. Data about progression patterns and locoregional management in patients included in the FLAURA trial were limited.[19]

In our study, a significantly longer TTD and a trend toward longer OS were identified in patients with fewer than three progressing sites and progression patterns (isolated vs. oligo vs. systemic) seem to be correlated with TTD, although without statistical significance. Of note, no difference in PFS was reported in these subgroups, highlighting once again the role of TTD as a more suitable measure of benefit in clinical practice.

Regarding safety, real-world studies allow investigators to detect AEs occurring in an unselected population and long-term toxicities.[15] In our study, more common any-grade AEs and toxicities management were in line with published data from randomized and real-world studies.[1,22,23]

In contrast, we observed a high rate of venous thromboembolism, which was the most frequent severe AE. In the FLAURA trial, the incidence of grade 3/4 venous thromboembolism was higher in the osimertinib arm compared with first-generation TKI (3% vs. 0.7%).[1] In AURA3 trial, pulmonary embolism was the most common serious AE reported with osimertinib (1.4% vs. 1% in the chemotherapy arm).[4] In the real-world ASTRIS study, grade 3 pulmonary embolism accounted for 2% of pretreated patients receiving osimertinib.[24] No significant incidence of thromboembolic events for patients treated with early-generation *EGFR*-TKIs emerged from pooled analysis of safety of phase II/III trials or from real-world studies.[25,26] Active thromboembolism or history of thromboembolic events were not exclusion criteria applied in pivotal trials.

These data suggest a thrombotic diathesis in patients receiving osimertinib, even more evident in our unselected population. Of note, safety metanalyses on *EGFR*-TKIs do not focus their attention on thrombotic events, and need further investigation.[27,28]

Globally, our results add consistence to efficacy and safety of osimertinib and may support the decision making process,

once additional options enter the clinical practice.[29,30] Indeed, the combination of erlotinib and ramucirumab demonstrated, in the RELAY trial, outcomes comparable with osimertinib, although patients with brain metastases at diagnosis were excluded.[31]

Finally, real-world studies allow monitoring the diagnostic-therapeutic pathway of patients treated in clinical practice, through the evaluation of specific indicators of effectiveness and appropriateness, hardly extractable from administrative health flow. The present study reports a shorter time to *EGFR* mutation status report compared with a previous study by our group in an overlapping population of Italian oncology centers. This could be due to a higher rate of reflex testing performed by pathologists at diagnosis, reflecting a learning curve in the diagnostic process.[26] On the contrary, time to treatment start was longer than historical data on early-generation TKIs, in part due to type of osimertinib access.

Mature overall survival, postprogression diagnostic-therapeutic pathway, long-term safety follow-up, and budget impact analysis will be future matter for further real-world evidence in this setting.

In conclusion, we confirm effectiveness and safety of osimertinib. However, thromboembolic events were more frequent than previously reported and need further investigation.

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Conflict of Interest

Valentina Guarneri: Eli Lilly, Novartis, Roche, Merck Sharp & Dohme (C/A), Eli Lilly, Novartis (H), Eli Lilly, Novartis, Bristol Meyers Squibb, Roche (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

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Figures and Tables

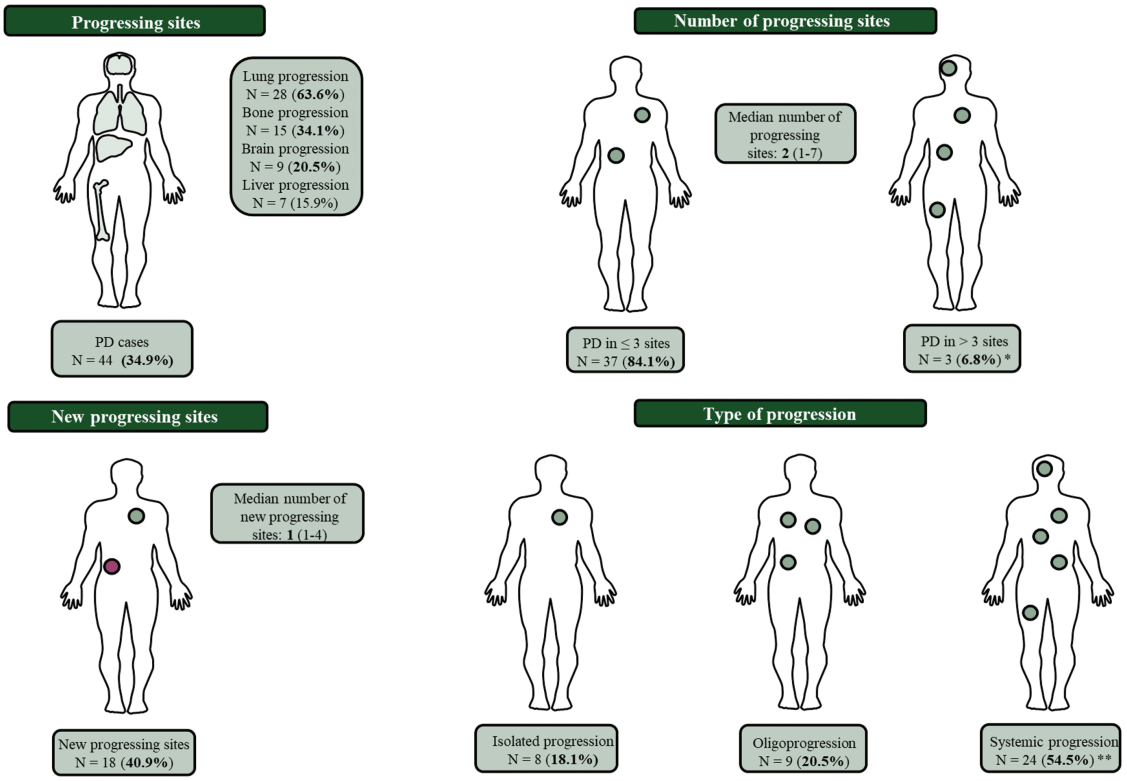

Figure 2. Progression patterns to first-line osimertinib. The most frequent progressing sites were lung, bone, and brain. Isolated PD: appearance or growth of one lesion; oligoprogression: PD in up to three lesions in two organs; systemic PD: appearance or progression in more than three lesions. *Progression pattern missing in four patients because of clinical progression or absence of radiological evaluation. **Type of progression missing in three patients because of clinical progression or absence of radiological valuation.Abbreviation: PD, progressive disease.

Table 1. Baseline clinical features of patients enrolled

Variable	*n*(%)
Number of cases	126 (100.0)
Age, median (range), yr	68.0 (30–88)
Gender	
Male	45 (35.7)
Female	81 (64.3)
Recurrent	
No	107 (84.9)
Yes	19 (15.1)
Smoking status	
Never smokers	69 (54.7)
Former smokers	43 (34.1)
Smokers	10 (7.9)
Unknown	4 (3.2)
Tumor histology	
Adenocarcinoma	120 (95.2)
Squamous cell carcinoma	3 (2.4)
Adenosquamous carcinoma	2 (1.6)
Unknown	1 (0.8)
Baseline *EGFR* mutation status	
Exon 19 deletion	63 (50.0)
Exon 21 L858R mutation	55 (43.7)
Rare	3 (2.4)
Complex	4 (3.3)
Unknown	1 (0.8)
Stage at diagnosis	
IIIB/IIIC	6 (4.8)
IVA	30 (23.8)
IVB	90 (71.4)
ECOG PS	
0–1	110 (87.3)
≥2	16 (12.7)
Symptoms at diagnosis	
Present	85 (67.5)
Absent	41 (32.5)
Charlson Comorbidity Index	
6	8 (6.3)
>6	118 (93.7)
n of metastatic sites at diagnosis	
<3	80 (63.5)
≥3	46 (36.5)
Brain metastases at diagnosis	
Present	38 (30.2)
Absent	88 (69.8)
Liver metastases at diagnosis	
Present	16 (12.7)
Absent	110 (87.3)
Bone metastases at diagnosis	
Present	59 (46.8)
Absent	67 (53.2)
Best response to osimertinib	
CR	0 (0)
PR	92 (73.0)
SD	29 (23.0)
PD	5 (4.0)
Unknown/not evaluated	0 (0)

Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NOS, not otherwise specified; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2. Univariate and multivariate analysis for progression free survival, overall survival and time to discontinuation according to patients features (Log-rank test and Cox proportional hazard)

Variable	*n*(%)	PFS univariate analysis, *p* value	PFS multivariate analysis		OS univariate analysis, *p* value	OS multivariate analysis		TTD univariate analysis, *p* value	TTD multivariate analysis	
			p value	HR (95% CI)		*p* value	HR (95% CI)		*p* value	HR (95% CI)
Number of cases	126 (100.0)									
Gender										
Male	45 (35.7)	.098	.120	1.753 (0.864–3.558)	.405	.268	1.705 (0.663–4.384)	.249	.167	1.744 (0.792–3.842)
Female	81 (64.3)									
Smoking status										
Smokers	53 (42.1)	.971	.901	0.958 (0.489–1.877)	.179	.118	0.402 (0.128–1.262)	.671	.468	0.746 (0.338–1.647)
Never smokers	69 (54.8)									
Unknown	4 (3.2)									
Age, years										
<65	50 (39.7)	.055	.287	0.697 (0.359–1.354)	.303	.923	0.955 (0.372–2.447)	.216	.722	0.873 (0.412–1.847)
≥65	76 (60.3)									
Baseline *EGFR* mutation status										
Exon 19 deletion	63 (50.0)	.852	.487	1.221 (0.695–2.146)	.679	.674	1.218 (0.486–3.052)	.848	.121	1.688 (0.871–3.272)
Exon 21 L858R mutation	55 (43.7)									
Others	7 (5.6)				.756					
Unknown	1 (0.8)									
Stage at diagnosis										
III-IVA	36 (28.6)	.230	.263	0.574 (0.217–1.520)	.096	.109	3.194 (0.772–13.209)	.104	.903	1.073 (0.344–3.352)
IVB	90 (71.4)									
ECOG PS										
0-1	110 (87.3)	.990	.463	0.673 (0.234–1.936)	.829	.829	1.171 (0.280–4.907)	.981	.355	0.574 (0.177–1.861)
≥2	16 (12.7)									
Symptoms at diagnosis										
Present	85 (67.5)	**.031**	.178	1.703 (0.785–3.695)	**.022**	.059	3.480 (0.955–12.678)	**.004**	**.028**	**3.035 (1.126–8.178)**
Absent	41 (32.5)									
Charlson Comorbidity Index										
6	8 (6.3)	.248	.833	1.160 (0.293–4.589)	.210	.498	0.539 (0.0901–3.223)	.146	.866	0.882 (0.206–3.772)
>6	118 (93.7)									
N. of metastatic sites at diagnosis										
<3	80 (63.5)	.151	.828	1.094 (0.488–2.448)	.182	**.036**	**3.602 (1.089–11.912)**	**.025**	.085	2.182 (0.899–5.297)
≥3	46 (36.5)									
Brain metastases at diagnosis										
Present	38 (30.2)	**.019**	**.035**	**2.382 (1.061–5.344)**	.223	.916	0.941 (0.303–2.919)	.076	.284	1.631 (0.666–3.995)
Absent	88 (69.8)									
Liver metastases at diagnosis										
Present	16 (12.7)	.364	.613	1.274 (0.499–3.249)	.515	.113	0.257 (0.0481–1.377)	.724	.557	0.724 (0.247–2.126)
Absent	110 (87.3)									

Table 2. Continued

Variable	*n*(%)	PFS univariate analysis, *p* value	PFS multivariate analysis		OS univariate analysis, *p* value	OS multivariate analysis		TTD univariate analysis, *p* value	TTD multivariate analysis	
			p value	HR (95% CI)		*p* value	HR (95% CI)		*p* value	HR (95% CI)
Bone metastases at diagnosis										
Present	59 (46.8)	.095	.158	1.813 (0.794–4.139)	.369	.004	0.167 (0.0490–0.570)	.254	.832	0.906 (0.366–2.245)
Absent	67 (53.2)									
Best response to TKI										
CR/PR	92 (73.0)	.808	.497	1.308 (0.603–2.834)	.285	.396	1.567 (0.556–4.414)	.984	.906	1.054 (0.443–2.508)
SD/PD	34 (27.0)									

Significant values are highlighted in bold.
Abbreviations: CI, confidence interval; coeff, coefficient; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation.

Table 3. Univariate and multivariate analysis for OS according to survival measures (log-rank and Cox proportional hazard)

Variable	*n*(%)	Univariate analysis OS, *p* value	Multivariate analysis OS		
			Coefficient	*p* value	HR (95% CI)
Number of cases	126 (100)				
PFS					
PFS <9 months	50 (39.7)	<.001	−0.884	.205	0.413 (0.105–1.620)
PFS ≥9 months	76 (60.3)				
TTD					
TTD <9 months	42 (33.3)	<.001	−1.933	.008	0.145 (0.0350–0.599)
TTD ≥9 months	84 (66.6)				

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation.

Table 4. Progression patterns to first-line osimertinib and univariate analysis for PFS, TTD, and OS according to progression pattern

Variable	*n*(%)	PFS, *p* value	TTD, *p* value	OS, *p* value
Number of cases	44 (100)			
Number of progressing sites				
Median (range)	2 (1–7)			
<3	31 (70.5)	.647	.050	.065
≥3	9 (20.4)			
Unknown/cinical PD	4 (9.1)			
New progressing sites				
Yes	18 (40.9)	.309	.075	.036
No	22 (50.0)			
Unknown/ cinical PD	4 (9.1)			
Number of new progressing sites				
Median (range)	1 (1–4)			
<3	39 (88.6)	<.001	<.001	<.001
≥3	1 (2.3)			
Unknown/cinical PD	4 (9.1)			
CNS progression				
Yes	9 (20.5)	.350	.251	.147
No	31 (70.4)			
Unknown	4 (9.1)			
Liver progression				
Yes	7 (15.9)	.948	.130	.138
No	33 (75.0)			
Unknown	4 (9.1)			
Lung progression				
Yes	28 (63.6)	.333	.515	.805
No	12 (27.3)			
Unknown	4 (9.1)			
Bone progression				
Yes	15 (34.1)	.713	.983	.977
No	25 (56.8)			
Unknown	4 (9.1)			
Adrenal progression				
Yes	6 (13.6)	.528	.784	.315
No	34 (77.3)			
Unknown	4 (9.1)			
Locoregional nodes progression				
Yes	6 (13.6)	.002	<.001	.097
No	34 (77.3)			

Table 4. Continued

Variable	*n*(%)	PFS, *p* value	TTD, *p* value	OS, *p* value
Unknown	4 (9.1)			
Distant nodes progression				
Yes	3 (6.8)	.279	.122	.140
No	37 (84.1)			
Unknown	4 (9.1)			
Type of progression				
Isolated	8 (18.2)	.775	.060	.245
Oligo	9 (20.5)			
Systemic	24 (54.5)			
Unknown	3 (6.8)			
Type of progression				
Isolated + Oligo	17 (38.6)	.475	.098	.111
Systemic	24 (54.5)			
Unknown	3 (6.9)			
Type of progression				
Isolated	8 (18.2)	.680	.018	.198
Oligo + Systemic	33 (75.0)			
Unknown	3 (6.8)			

Abbreviations: NA, not applicable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; oligo, oligoprogression; TTD, time to treatment discontinuation.

Table 5. Diagnostic-therapeutic pathway

Variable	G1/G2, *n* (%)
Number of cases *n* (%)	126 (100.0)
Time from biopsy to pathologic report, median (range), days	8 (0–55)
Time from pathologic report to *EGFR* mutation report, median (range), days	8 (–3.00 to 1,746)
Time to treatment start from *EGFR* mutation report, median (range), days	20 (–1.00 to 3,371)
No recurrent	107 (84.9)
Time from biopsy to pathologic report, median (range), days	7.0 (2–55)
Time from pathologic report to *EGFR* mutation report, median (range), days	8 (–3.00 to56)
Time to treatment start from *EGFR* mutation report, median (range), days	17 (–1.00 to301)
Time to treatment start (days), median (range):	
H-class/AIFA prescription	12 (0–301)
CNN/off label	24 (–1 to131)
Time to treatment start, median (range), days	
No COVID time	18.5 (–1 to17)
COVID-time (March–May 2020)	11 (1–1,318)

Abbreviations: AIFA, Agenzia Italiana del Farmaco, Italian Drug Agency (H class/AIFA register drugs which have been reimbursed by the national health system for hospital distribution and which have been listed in the innovative drug register); CNN, class C non-negotiated (drugs which have received the marketing authorization but costs have not yet been negotiated); *EGFR*, epidermal growth factor receptor.

Table 6. Locoregional palliative treatments

Variable	*n*(%)
Number of cases	126 (100)
Any locoregional treatment	39 (31.0)
Timing	
Within a month from starting treatment	21 (53.8)
During treatment	16 (41.0)
Time to first locoregional treatment, median (range), mo	8.5 (2.1–17.7)
Missing	2 (5.1)
Locoregional terapies (excluding brain)	
Yes	30 (23.8)
No	96 (76.2)
Type of locoregional therapy	
RT	24 (80.0)
Surgery	5 (16.7)
Surgery + RT	1 (3.3)
Brain locoregional therapy	
Yes	20 (15.9)
No	106 (84.1)
Type of brain locoregional therapy	
Stereotactic body radiation therapy	11 (55.0)
Whole brain RT	8 (40.0)
Surgery	1 (5.0)

Abbreviations: RT, radiotherapy.

Table 7. Adverse events reported with osimertinib.

Adverse event	Any grade, *n* (%)	G3/G4, *n* (%)	G1/G2, *n* (%)
Any	**110 (87.3)**	**42 (33.3)**	**68 (54.0)**
ILD/pneumonitis	12 (9.5)	3 (2.4)	9 (7.1)
Diarrhea	**49 (38.9)**	4 (3.2)	45 (35.7)
Stomatitis	17 (13.5)	1 (0.8)	16 (12.7)
Keratitis	7 (5.6)	0 (0.0)	7 (5.6)
Rash	**42 (33.3)**	2 (1.6)	40 (31.7)
Dry skin	**24 (19.0)**	0 (0.0)	24 (19.0)
Paronychia	**33 (26.2)**	1 (0.8)	32 (25.4)
Pruritus	12 (9.5)	0 (0.0)	12 (9.5)
QTcProlonged	2 (1.6)	1 (0.8)	1 (0.8)
Platelet count decrease	18 (14.3)	3 (2.4)	15 (11.9)
Leucopenia	17 (13.5)	1 (0.8)	16 (12.7)
Neutropenia	9 (7.1)	0 (0.0)	9 (7.1)
Venous thromboembolism	**12 (9.5)**	**10 (7.9)**	**2 (1.6)**
Creatinine increased	**26 (20.6)**	**0 (0.0)**	**26 (20.6)**
Heart failure	**2 (1.6)**	**1 (0.8)**	**1 (0.8)**
Arterial thromboembolism	**3 (2.4)**	**2 (1.6)**	**1 (0.8)**
Myocardial infarction	2 (1.6)	2 (1.6)	0 (0)
Atrial fibrillation	2 (1.6)	0 (0.0)	2 (1.6)
Pericardial effusion	2 (1.6)	0 (0.0)	2 (1.6)
Anemia	7 (5.6)	0 (0.0)	7 (5.6)
Asthenia	9 (7.1)	0 (0.0)	9 (7.1)
AST and ALT increased	10 (7.9)	0 (0.0)	10 (7.9)
Nausea	7 (5.6)	1 (0.8)	6 (4.8)
Oral dysesthesia	1 (0.8)	0 (0.0)	1 (0.8)
Hyponatriemia	3 (2.4)	0 (0.0)	3 (2.4)
Oral hemorrhage	1 (0.8)	0 (0.0)	1 (0.8)
Bilirubin increase	1 (0.8)	0 (0.0)	1 (0.8)
Skin ulceration	2 (1.6)	1 (0.8)	1 (0.8)
Alopecia	2 (1.6)	0 (0.0)	2 (1.6)
Endocarditis	1 (0.8)	1 (0.8)	0 (0)
Hemorrhoids	2 (1.6)	1 (0.8)	1 (0.8)
Gastric pyrosis	2 (1.6)	0 (0.0)	2 (1.6)
Abdominal pain	1 (0.8)	0 (0.0)	1 (0.8)
Constipation	2 (1.6)	0 (0.0)	2 (1.6)
Peripheral sensory neuropathy	1 (0.8)	0 (0.0)	1 (0.8)

Significant values are highlighted in bold.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; G3/G4, grade 3/grade 4; ILD, Interstitial Lung Disease; QTcProlonged, electrocardiogram QT corrected interval prolonged.

Table 8. Univariate analysis of baseline patient characteristics predicting venous thromboembolism

Variable	VTE + any grade *n*(%)	VTE – any grade *n*(%)	Univariate analysis *p* value	VTE + G3–G4 *n* (%)	VTE – G3-G4 *n* (%)	Univariate analysis *p* value
Number of cases	12 (100)	114 (100)		10 (100)	116 (100)	
Age, years						
<65	8 (66.7)	42 (36.8)		6 (60)	44 (37.9)	
≥65	4 (33.3)	72 (63.2)	.0624	4 (40)	72 (62.1)	.1932
CCI						
6	2 (16.7)	6 (5.3)		2 (20)	6 (5.2)	
>6	10 (83.3)	108 (94.7)	.7570	8 (80)	110 (94.8)	.1229
Number of metastatic sites						
<3	7 (58.3)	73 (64.0)		5 (50)	75 (64.7)	
≥3	5 (41.7)	41 (36.0)	.7570	5 (50.0)	41 (35.3)	.4952
ECOG PS						
0–1	10 (83.3)	100 (87.7)		9 (90.0)	101 (87.1)	
≥2	2 (16.6)	14 (12.3)	.6496	1 (10.0)	15 (12.9)	1.0000

Abbreviations: VTE, venous thromboembolism; +, present; -, absent; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group Performance Status; N, number.

Table 9. Toxicity management

Variable	*n*(%)
Number of cases	126 (100.0)
Time to first toxicity, median (range), days	45 (1–393)
Osimertinib interruption for toxicity	
Yes	25 (19.8)
No	101 (80.2)
Time of maximum osimertinib interruption, median (range), days	7 (2–54)
Osimertinib permanent interruption for toxicity	
Yes	9 (7.1)
No	117 (92.9)
Osimertinib temporary interruption related AEs	
Diarrhea	4 (3.2)
Heart failure	1 (0.8)
Fatigue	1 (0.8)
Paronychia	2 (1.6)
Platelet count decrease	6 (4.8)
Anemia	1 (0.8)
Rash	3 (2.4)
Bilirubin increase	1 (0.8)
Neutropenia	2 (1.6)
Leucopenia	2 (1.6)
ILD/pneumonitis	2 (1.6)
Stomatitis	1 (0.8)
Keratitis	1 (0.8)
QT prolongation	1 (0.8)
Hemorrhoids	1 (0.8)

Table 9. Continued

Variable	*n*(%)
Osimertinib permanent interruption related AEs	
Venous thromboembolism	1 (0.8)
Arterial thromboembolism	2 (1.6)
ILD/Pneumonitis	3 (2.4)
Osimertinib dose reduction	
Yes	11 (8.7)
No	115 (91.3)
Toxicity causing osimertinib dose reduction	
Diarrhea	2 (1.6)
Oral dysesthesia	1 (0.8)
Hearth failure	1 (0.8)
Platelet count decrease	3 (2.4)
Leucopenia	2 (1.6)
Neutropenia	1 (0.8)
Rash	1 (0.8)
Keratitis	1 (0.8)
QT interval prolongation	1 (0.8)

Sum is not 100% because some cases underwent more than one toxicity.
Abbreviations: AEs, adverse events; ILD, interstitial lung disease.

Table 10. Participating centers

Center	City	Adress
Veneto Institute of Oncology IOV – IRCCS – coordinating center	Padua	Via Gattamelata, 64, 35128, Padua (PD), Italy
Regina Elena National Cancer Institute - IRCCS	Rome	Via Elio Chianesi, 53, 00144, Rome (RM), Italy
National Cancer Institute Centro di Riferimento Oncologico (CRO) – IRCCS	Aviano	Via Franco Gallini, 2, 33081, Aviano (PN), Italy.
Azienda Sanitaria Universitaria Integrata of Udine, Santa Maria della Misericordia Hospital	Udine	Via Pozzuolo, 330, 33100 Udine (UD), Italy
Azienda Ospedaliera Universitaria Integrata di Verona	Verona	Piazzale Aristide Stefani, 1, 37126 Verona (VR), Italy
Azienda Unità Locale Socio Sanitaria (AULSS) 2 Marca Trevigiana, Ca' Foncello Hospital	Treviso	Piazzale Ospedale, 1, 31100, Treviso (TV), Italy
Azienda Ospedaliera Policlinico Universitario "G. Martino"	Messina	Via Consolare Valeria, 1, 98124 Messina (ME), Italy
AULSS 3 Serenissima, Angelo Hospital	Venice-Mestre	Via Paccagnella, 11, 30174, Venezia (VE), Italy
AULSS 6 Euganea, South Padua Hospital	Monselice	Via Albere, 30, 35043 Monselice (PD), Italy

Abbreviations: IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico, Scientific Institute for Research, Hospitalization and Health Care; AULSS, Azienda Unità Locale Socio Sanitaria, Local Health Unit.