Original Article

# Upfront osimertinib and as sequential therapy in patients with *EGFR*-mutant non-small cell lung cancer (NSCLC): benefit across patients groups in a real-world retrospective cohort—the smile study

**Edouard Auclin[1,2], Pauline Du Rusquec[3], Victor Albarran-Artahona[4], Frank Aboubakar[5], Helena Gerber[6], Nicolas Epaillard[7], Gonzalo Recondo[8], Andrea De Giglio[9], Hugo Berthou[1,2], Juan Carlos Laguna[4], Teresa Gorria[4], Juan Bautista Blaquier[8], Beatriz Jimenez-Munarriz[10], Marco Tagliamento[11], Alessandro Di Federico[9], Gianluca Sacco[11], José Minatta[8], Nicolas Girard[3], Teresa Moran-Bueno[12], Rafael Lopez-Castro[13], Benjamin Besse[6], Laura Mezquita[4,14,15]**

[1]Department of Medical Oncology, Hôpital Européen Georges Pompidou, AP-HP, Université Paris Cité, France; [2]Department of Oncology, Institut Bergonié, Bordeaux, France; [3]Thorax Institute Curie Montsouris, Institut Curie, Paris, France; [4]Department of Medical Oncology, Hospital Clinic de Barcelona, Barcelona, Spain; [5]Université de Louvain, Brussels, Belgium; [6]Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France; [7]Department of Oncology, Centre Hospitalier of French Polynesia, Pirae, Tahiti, French Polynesia; [8]Department of Medical Oncology, Center for Medical Education and Clinical Research (CEMIC), Buenos Aires, Argentina; [9]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [10]Department of Oncology, HM Hospitales, Madrid, Spain; [11]Department of Oncology, IRCCS Ospedale Policlinico San Martino and University of Genova, Genova, Italy; [12]Department of Medical Oncology, ICO de Badalona, Barcelona, Spain; [13]Department of Medical Oncology, Hospital Clinico Universitario de Valladolid, Valladolid, Spain; [14]Laboratory of Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain; [15]Department of Medicine, University of Barcelona, Barcelona, Spain

*Contributions:* (I) Conception and design: E Auclin, L Mezquita, B Besse; (II) Administrative support: E Auclin, L Mezquita, B Besse, P Du Rusquec; (III) Provision of study materials or patients: P Du Rusquec, V Albarran-Artahona, F Aboubakar, H Gerber, N Epaillard, G Recondo, A De Giglio, H Berthou, JC Laguna, T Gorria, JB Blaquier, B Jimenez-Munarriz, M Tagliamento, A Di Federico, G Sacco, J Minatta, N Girard, T Moran-Bueno, R Lopez-Castro; (IV) Collection and assembly of data: P Du Rusquec, V Albarran-Artahona, F Aboubakar, H Gerber, N Epaillard, G Recondo, A De Giglio, H Berthou, JC Laguna, T Gorria, JB Blaquier, B Jimenez-Munarriz, M Tagliamento, A Di Federico, G Sacco, J Minatta, N Girard, T Moran-Bueno, R Lopez-Castro; (V) Data analysis and interpretation: E Auclin, L Mezquita, B Besse; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Laura Mezquita, MD, PhD. Department of Medical Oncology, Hospital Clinic de Barcelona, Barcelona, Spain; Laboratory of Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain; Department of Medicine, University of Barcelona, Barcelona, Spain; Calle Villaroel 170, Escala 2, Planta 5, Barcelona 08036, Spain. Email: lmezquita@clinic.cat.

**Background:** Osimertinib is the preferred first-line (L1) treatment for epidermal growth factor receptor-mutant (m*EGFR*) advanced non-small cell lung cancer (aNSCLC). Intensification of L1 with chemotherapy or amivantamab has shown improved outcomes at the cost of increased toxicity, raising questions about the optimal patients selection. A sequence involving first-generation tyrosine kinase inhibitor (TKI) (1G) followed by osimertinib might be considered. This study assessed the efficacy of these therapeutic strategies based on the clinical profiles of a real-life cohort.

**Methods:** Retrospective multicenter study including consecutive patients with m*EGFR* (ex19/ex21) aNSCLC treated with either osimertinib or the sequence of 1G followed by osimertinib ("sequence group"). Central nervous system (CNS) metastases were permitted. We assessed progression-free survival (PFS) of the global strategy (PFSglob) defined as the time between L1 start and progression after L2 treatment or death. Secondary endpoints were overall survival (OS), PFS of the L1 treatment, and tumor response according to each center daily practice [objective response rate (ORR) and disease control rate (DCR)].

**Results:** A total of 300 patients with m*EGFR* aNSCLC were enrolled (n=161 in the osimertinib group, n=139 in the sequence group). Baseline characteristics in both groups were similar except for baseline CNS

involvement (41% in osimertinib-group *vs.* 25%), poor performance status (PS) ≥2 (21% *vs.* 10%) and high-tumor burden (TB), defined as >3 metastatic sites or CNS involvement (51% *vs.* 35%). The osimertinib group had longer median first-line PFS (PFS1; 19.0 *vs.* 16.8 months, P=0.03). The sequence group had improved PFSglob *vs.* the osimertinib-group (32.4 *vs.* 26.5 months, P=0.04) but this difference was not significant in multivariate Cox analysis (adjusted on age, smoking history, number of metastatic sites, liver, CNS and soft tissue metastasis, and PS) nor after a propensity score matching analysis, osimertinib upfront was associated with better PFSglob in the poor-prognosis groups: high-TB, CNS or liver involvement and poor PS.

**Conclusions:** In this real-life study we showed that osimertinib upfront demonstrated prolonged PFS1 *vs.* 1G followed by osimertinib, with better PFSglob in patients with poor-prognosis m*EGFR* aNSCLC. This study raises the question of patients selection and treatment tailoring for the first line management of metastatic m*EGFR* non-small cell lung cancer (NSCLC).

**Keywords:** Epidermal growth factor receptor (EGFR); non-small cell lung cancer (NSCLC); osimertinib; tyrosine kinase inhibitor (TKI)

Submitted Sep 23, 2024. Accepted for publication Apr 08, 2025. Published online Jul 21, 2025.
doi: 10.21037/tlcr-24-881
**View this article at:** https://dx.doi.org/10.21037/tlcr-24-881

## Introduction

Lung cancer stands as the leading cause of cancer-related death worldwide (1). The identification of driver molecular alterations in oncogenes involved in lung cancer development marked a major breakthrough in therapeutic strategy. The subsequent development of various generations of targeted therapies demonstrated improvements in survival and quality of life, with a favorable safety profile in patients harboring such alterations.

### Highlight box

**Key findings**

- Osimertinib should be prescribed upfront for patients with advanced epidermal growth factor receptor (*EGFR*)-mutant non-small cell lung cancer (NSCLC) who have central nervous system (CNS) or liver metastases, or a poor performance status.

**What is known and what is new?**

- Osimertinib, as well as first- and second-generation tyrosine kinase inhibitors, are recommended as possible first-line treatments for *EGFR*-mutant NSCLC.
- Intensification of first-line treatment (e.g., chemotherapy with osimertinib or amivantamab-lazertinib) can be proposed for certain subgroups.

**What is the implication, and what should change now?**

- A sequential treatment strategy could be explored for patients with a low tumor burden or no CNS metastases.

Epidermal growth factor receptor (EGFR) mutations are found in approximately 10–15% of advanced non-small cell lung cancer (aNSCLC) cases in European populations and 50% in Asian populations. The two most prevalent alterations of the *EGFR* gene are exon 19 deletions and exon 21 L858R mutations (2). Tumors with these mutations exhibit sensitivity to EGFR tyrosine kinase inhibitors (TKIs). The initial therapies showing a survival benefit over chemotherapy in patients with *EGFR*-mutant (m*EGFR*) advanced NSCLC were first-generation TKIs (erlotinib, gefitinib) (3-5). Subsequently, second and third-generation TKIs were developed.

Osimertinib, a third-generation TKI, was initially administered upon progression on erlotinib or gefitinib if patients developed the T790M resistance mutation (6). Moreover, osimertinib demonstrated superiority over first-generation TKIs, including in brain metastases, in the first-line setting in 2018 becoming the preferred upfront therapy in this population since then (7,8).

Recently, new strategies intensifying first-line treatment with osimertinib plus platinum-based chemotherapy or lazertinib with amivantamab have been reported with improved progression-free survival (PFS) (9,10). However, these combinations also induce more toxicity, raising questions about the optimal patient selection. For now, osimertinib remains the standard of care.

Indeed, in a selected population, treatment with osimertinib as monotherapy upfront, and particularly as

sequential therapy, has demonstrated the potential for achieving significantly prolonged PFS and overall survivals (OS) (11). Although the use of osimertinib as sequential therapy in T790M+ tumors is not a common practice, the sequence strategy involving the use of a first-generation TKI followed by osimertinib (if T790M+ mutation is present) could still be considered as an option for certain patients. This is supported by the recent findings from the APPLE trial, which demonstrated promising outcomes in this specific patient group (12). Unfortunately, the specific profile of this "responder" population remains unknown. Exploring subgroups potentially benefiting of sequential anti-EGFR treatment is clinically interesting as it allows patients to stay on oral and well tolerated drugs as long as possible. In the real-world international multicenter SMILE study, we aimed to assess the efficacy of osimertinib upfront and as sequential therapy based on the clinical profile of patients with m*EGFR* advanced NSCLC. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-881/rc).

## Methods

### *Study design and population*

Retrospective multicenter study (15 centers in France, Italy, Spain, Belgium and Argentina) enrolling patients with histologically confirmed untreated advanced NSCLC harboring exon 19 or 21 *EGFR* sensitizing mutations treated with osimertinib upfront or as sequential therapy after 1$^{st}$ or 2$^{nd}$ generation of EGFR-TKI from November 2020 to July 2022. Central nervous system (CNS) metastases were permitted.

We classified the population in two groups: the sequence group that received first generation TKI followed by osimertinib, and the osimertinib group that received osimertinib upfront.

Patients' follow-up was conducted in according to each centers' daily practice until data collection.

Data were registered in an electronic Case Report Form (CRF) from each patients' medical record. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. This study was approved by the internal ethics committee at Gustave Roussy (IRB number 2021-01) and in each center according to the local rules. No consent to participate was needed for participation as it is a retrospective study.

### *Endpoint definition*

The primary endpoint was the PFS of the global strategy (PFSglob) defined as the time between the initiation of first line and the progression or death under second line, whichever occurred first. Secondary endpoints included first-line PFS (PFS1) and OS. PFS1 was defined as the time between the start of first line and progression or death under first line treatment, whichever occurred first. OS was defined as the time between the initiation of first line treatment start and death from any cause (Figure S1).

Tumor response was evaluated according to each center's daily practice. The disease control rate (DCR) was defined as the percentage of patients who achieved complete response (CR), partial response (PR) and stable disease (SD) and objective response rate (ORR) was defined as the percentage of patients who achieved CR or PR.

### *Statistical analysis*

Median values (interquartile range) and frequencies (percentage) were provided for descriptions of continuous and categorical variables, respectively. Mean and proportions were compared using the Student's *t*-test and chi-square test (or Fisher's exact test, if appropriate), respectively.

PFSglob, PFS1 and OS were estimated using the Kaplan-Meier method and described using median values with their 95% confidence intervals (95% CIs) or percentage at key time points. Follow-up was calculated using the reverse Kaplan-Meier method.

Variables associated with survival were assessed with univariate and multivariate Cox models.

A sensitivity analysis was performed to consider the imbalance between the two treatment groups. Hence, we constructed a propensity score using the MatchIt package of R. In this score we included all statistically imbalanced clinical characteristics between the two groups and matched patients from the two groups according to the propensity score (1:1 matching). We then validated the endpoints analysis on this matched cohort.

We analyzed the following prognostic groups: high/low TB (high-TB; >3 metastatic sites or CNS involvement), presence/absence of CNS involvement, poor performance status (PS ≥2) *vs.* good (PS 0–1), and presence/absence of liver metastases.

Regarding missing data, no imputation was made, and variables with more than 20% of missing data were

 

discarded.

All statistical analyses were performed with R studio, P values <0.05 were considered statistically significant.

## Results

### *Study population*

A total of 300 patients with m*EGFR* advanced NSCLC were enrolled in our study (Figure S2). In this cohort 66.3% were female, 58.3% non-smokers, with 51.3% older than 65 years (*Table 1*). Osimertinib was administered as the first-line treatment in 161 patients, while 139 patients received osimertinib in the second-line setting (sequence group). Baseline CNS involvement was observed in 33.8% of the patients and liver metastasis in 14.1% of the patients.

In the sequence group, first-line TKI was gefitinib, erlotinib, afatinib or dacomitinib in 35.3%, 33.8%, 26.6% and 0.7% of the patients, respectively. Baseline characteristics in both groups were similar except for baseline CNS involvement (41.2% in osimertinib-group *vs.* 25.2%), poor PS ≥2 (21.3% in osimertinib-group *vs.* 9.2%) and high tumor burden (TB) (51.3% in osimertinib-group *vs.* 34.6%).

The characteristics of the population included in the propensity score is summarized in Table S1.

### *Survival endpoints*

After a follow up of 36.1 months (95% CI: 32.0–40.5), median PFSglob was 30.4 months (95% CI: 26.5–34.2), while the median OS and PFS1 were 41.2 months (95% CI: 35.2–51.2) and 18.0 months (95% CI: 16.0–20.4), respectively (*Table 2*).

The median PFSglob was 26.5 months [95% CI: 20.9–not reached (NR)] in the osimertinib group versus 32.4 months (95% CI: 29.4–38.4) in the sequence group (P=0.04). The 18 months PFSglob rates were 56.2% (95% CI: 47.9–65.9) and 65.9% (95% CI: 58.4–74.3) in the osimertinib and sequence group, respectively (*Table 2*).

Median PFS1 was 19.0 months in the osimertinib-group *vs.* 16.8 months in the sequence-group (P=0.03), and median OS was NR in the osimertinib group *vs.* 43.8 months in the sequence-group (P=0.006). The 18 months rates are displayed in *Table 2*.

In multivariable analysis, after adjustment on age, smoking history, number of metastatic sites, liver, CNS and soft tissue metastasis, and PS, we did not find any difference between osimertinib upfront and second line use for the PFSglob and OS (sequence *vs.* osimertinib: HR for PFSglob 0.89, 95% CI: 0.59–1.35, P=0.59; HR for OS 0.71, 95% CI: 0.44–1.17, P=0.18). There was a benefit in the use of osimertinib upfront in term of PFS1 (sequence *vs.* osimertinib: HR for PFS1 1.93, 95% CI: 1.34–2.76). These results are summarized in Table S2. In the sensitivity analysis using a propensity score, no difference in survival endpoint was observed between the two treatment groups (*Table 3*).

### *Response endpoints*

Two hundred and five patients were evaluable for response. In this population, ORR was 83.7%, and DCR was 96.9% (*Table 2*). No differences were observed in terms of ORR between the osimertinib and the sequence groups (80.9% *vs.* 87.0%, respectively; P=0.15). DCR was also comparable (95.5% in osimertinib group *vs.* 98.6% in sequence group, P=0.18).

No difference in response rates was observed in the matched propensity score cohort (*Table 3*).

### *Subgroups analysis*

Finally, we explored the effect of osimertinib upfront in subgroups of interest. Osimertinib upfront was associated with better PFSglob in the poor-prognosis groups (*Figure 1*): high-TB, CNS or liver involvement and poor PS. In contrast, the sequence group had improved PFSglob in patients with low-TB (38.5 *vs.* 35.5 months, P=0.05), no liver (36 *vs.* 30 months, P=0.02) or CNS involvement (37.9 *vs.* 35.5 months, P=0.07). These results are summarized in Table S3.

## Discussion

In this retrospective international multicenter study, we observed similar outcomes in a cohort of 300 patients treated for m*EGFR* NSCLC when comparing upfront osimertinib with a sequence strategy in term of global PFS. However, the use of osimertinib in the first-line setting demonstrated superiority in term of PFS1 compared to a sequence strategy. Poor prognosis subgroups, including patients with poor PS, CNS and liver involvement, and high TB, derived greater benefit from upfront osimertinib. In contrast, the sequence strategy showed similar outcomes in patients without CNS involvement or low TB.

**Table 1** Baseline characteristics of the study population

| Characteristics | Overall sample (N=300) | Osimertinib group (N=161) | Sequence group (N=139) | P |
|---|---|---|---|---|
| Age, >65 years | 154 (51.3) | 83 (51.6) | 71 (51.1) | 0.93 |
| Gender, female | 199 (66.3) | 98 (60.9) | 101 (72.7) | 0.03 |
| Smoking history | | | | 0.52 |
| Former | 96 (33.3) | 57 (35.8) | 39 (30.2) | |
| Never smoker | 168 (58.3) | 88 (55.3) | 80 (62.0) | |
| Current | 24 (8.4) | 14 (8.9) | 10 (7.8) | |
| Missing | 12 | 2 | 10 | |
| Type of EGFR mutation[†] | | | | |
| Exon 19 | 195 (65.0) | 99 (61.5) | 96 (69.1) | 0.17 |
| Exon 21 | 106 (35.3) | 59 (36.6) | 47 (33.8) | 0.61 |
| Exon 20 co-mutation | 13 (4.3) | 7 (4.3) | 6 (4.3) | 0.99 |
| *TP53* co-mutation[†] | | | | <0.01 |
| Not performed | 142 (51.6) | 63 (42.0) | 79 (63.2) | |
| Yes | 27 (9.8) | 18 (12.0) | 9 (7.2) | |
| Missing | 25 | 11 | 14 | |
| Stage at EGFR at time of initiation of TKI[†] | | | | – |
| IV | 276 (94.5) | 149 (94.3) | 127 (94.8) | |
| Missing | 8 | 3 | 5 | |
| Number of metastatic sites[†] | | | | 0.71 |
| >3 | 68 (23.2) | 38 (24.1) | 30 (22.2) | |
| Missing | 7 | 3 | 4 | |
| Metastatic location[†] | | | | |
| CNS | 101 (33.8) | 66 (41.2) | 35 (25.2) | <0.01 |
| Missing | 1 | 1 | 0 | |
| Liver | 42 (14.1) | 23 (14.4) | 19 (13.8) | 0.88 |
| Missing | 2 | 1 | 1 | |
| Pleura | 100 (33.6) | 52 (32.3) | 48 (35.0) | 0.62 |
| Missing | 2 | 0 | 2 | |
| Lung | 156 (52.0) | 77 (47.8) | 79 (56.8) | 0.12 |
| Bone | 156 (52.0) | 84 (52.2) | 72 (51.8) | 0.95 |
| Soft tissue | 7 (2.3) | 4 (2.5) | 3 (2.2) | >0.99 |
| Missing | 2 | 1 | 1 | |
| Tumor burden[†] | | | | <0.01 |
| High | 128 (43.5) | 81 (51.3) | 47 (34.6) | |
| Missing | 6 | 3 | 3 | |
| ECOG PS[†] | | | | 0.01 |
| ≥2 | 39 (16.3) | 30 (21.3) | 9 (9.2) | |
| Missing | 61 | 20 | 41 | |

Data are presented as n (%) or number. [†], patients could have comutations. Tumor burden, defined as high if >3 metastatic sites or CNS involvement. CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

**Table 2** Survival and response endpoints in the overall cohort and according to treatment group before the propensity score matching

| Variables | Whole cohort (n=300) | Osimertinib (n=161) | Sequence (n=139) | P |
|---|---|---|---|---|
| PFSglob | | | | 0.04 |
| Median, months | 30.4 (26.5–34.2) | 26.5 (20.9–NR) | 32.4 (29.4–38.4) | |
| 18 months rate, % | 71.7 (66.5–77.2) | 56.2 (47.9–65.9) | 65.9 (58.4–74.3) | |
| 24 months rate, % | 60.1 (54.3–66.4) | 55.5 (47.1–65.2) | 44.7 (37.0–54.0) | |
| OS | | | | <0.01 |
| Median, months | 41.2 (35.2–51.2) | NR (25.9–NR) | 43.8 (38.7–54.0) | |
| 18 months rate, % | 83.0 (78.7–87.5) | 74.9 (68.0–82.4) | 91.4 (86.8–96.2) | |
| 24 months rate, % | 70.9 (65.5–76.7) | 62.5 (54.2–72.0) | 79.5 (73.0–86.6) | |
| PFS1 | | | | 0.03 |
| Median, months | 18.0 (16.0–20.4) | 19.0 (16.1–26.5) | 16.8 (14.1–19.8) | |
| 18 months rate, % | 50.0 (44.4–56.3) | 53.3 (45.5–62.4) | 47.1 (39.4–56.3) | |
| ORR, % | 83.7 | 80.9 | 87.0 | 0.15 |
| DCR, % | 96.9 | 95.5 | 98.6 | 0.18 |

Data in parentheses are presented as (95% CI). CI, confidence interval; DCR, disease control rate; NR, not reached; ORR, objective response rate; OS, overall survival; PFS1, progression-free survival for first line; PFSglob, progression-free survival of the global strategy.

**Table 3** Survival and response endpoints in the overall cohort and according to treatment group after the propensity score matching

| Variables | Propensity matched cohort (n=192) | Osimertinib (n=96) | Sequence (n=96) | P |
|---|---|---|---|---|
| PFSglob | | | | 0.30 |
| Median, months | 31.2 (25.9–37.3) | 30.1 (23.9–NR) | 32.4 (27.1–38.5) | |
| 18 months rate, % | 73.0 (66.7–79.8) | 64.7 (55.0–76.1) | 80.2 (72.6–88.6) | |
| 24 months rate, % | 60.3 (53.3–68.2) | 58.2 (47.9–70.6) | 63.2 (54.2–73.7) | |
| OS | | | | 0.10 |
| Median, months | 43.4 (38.1–59.1) | NR (26.4–NR) | 44.9 (39.4–64.2) | |
| 18 months rate, % | 85.2 (80.2–90.5) | 78.1 (69.8–87.4) | 91.7 (86.3–97.4) | |
| 24 months rate, % | 72.5 (66.0–79.6) | 67.2 (57.3–78.7) | 77.8 (69.8–86.7) | |
| PFS1 | | | | <0.01 |
| Median, months | 17.8 (15.3–21.2) | 23.3 (16.1–NR) | 16.5 (13.0–20.4) | |
| 18 months rate, % | 49.4 (42.6–57.4) | 55.2 (45.4–67.0) | 44.7 (35.7–56.0) | |
| ORR, % | 83.5 | 79.6 | 87.4 | 0.15 |
| DCR, % | 97.9 | 97.8 | 97.9 | >0.99 |

Data in parentheses are presented as (95% CI). CI, confidence interval; DCR, disease control rate; NR, not reached; ORR, objective response rate; OS, overall survival; PFS1, progression-free survival for first line; PFSglob, progression-free survival of the global strategy.

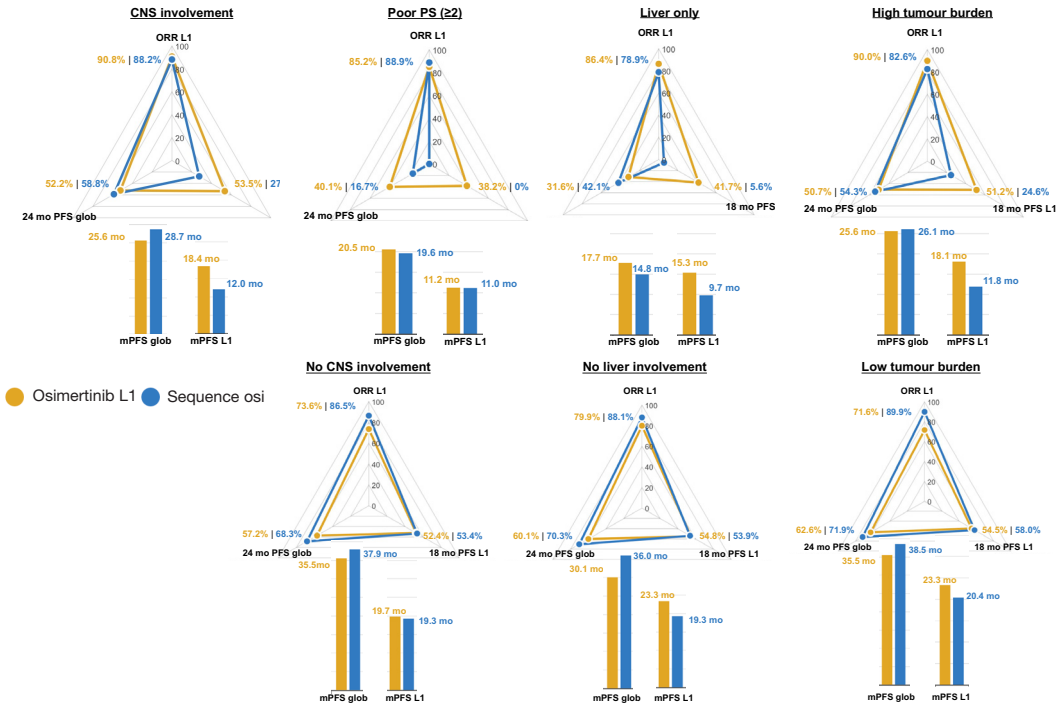


**Figure 1** Subgroups analysis results (response and survival endpoints). For each subgroup of interest (presence or absence of CNS or liver metastasis, poor PS, and high/low tumor burden), the radar plots represent the ORR and PFS rate at 18 months for the first line, and the 24 months-rate for the PFSglob. The bar plots represent the mPFSglob and mPFS1. CNS, central nervous system; L1, first line; mPFS, median progression-free survival; mPFS1, median progression-free survival for first line; mPFSglob, median progression-free survival of the global strategy; ORR, objective response rate; PFS, progression-free survival; PFSglob, global progression-free survival; PS, performance status.

Until now, the current standard of care is upfront osimertinib, established by the phase III FLAURA trial in 2018 (7,8). In this trial osimertinib upfront demonstrated improvements in PFS (median 18.9 *vs.* 10.2 months for standard EGFR-TKI), OS and CNS activity with a similar response rate. However, in this study only 47% of the patients in the osimertinib arm received osimertinib as second line treatment, which was the standard of care at that time.

The outcomes of our cohort closely resemble those of the FLAURA study in term of median PFS1 in the osimertinib group and response rates. Of note, our sequence group demonstrated superior outcomes compared to FLAURA, with higher median PFS1 (16.8 *vs.* 10.2 months) and OS (43.8 *vs.* 31.8 months). At 24 months, 79% of the patients from our sequence group were still alive compared to 59% in the standard treatment group in the FLAURA trial. Unfortunately, we lack results for patients from the FLAURA trial who underwent the sequence (standard EGFR-TKI followed by osimertinib).

In line with our cohort, a recent randomized trial exploring serial ctDNA monitoring and sequential strategy in m*EGFR* NSCLC (12), the sequence arm demonstrated comparable survival outcomes to the upfront osimertinib group, with a median OS of 42.8 months, identical to the OS observed in our cohort. Similar results were found in another retrospective cohort in 74 Japanese patients (13).

The comparison with these randomized trials suggests that our cohort, despite being in a real-life setting, included a population comparable to pivotal trials in this scenario. Another study assessing the outcomes of osimertinib in a real-world cohort found similar survival benefit than ours (14).

However, it is important to note the potential selection bias in our retrospective data collection.

Initially, the sequence group had a better PFSglob compared to the osimertinib group, attributed to imbalanced poor prognostic factors. After applying a

propensity score, the sequence group showed similar PFSglob to the osimertinib group. Similarly, multivariable Cox models, adjusting for imbalanced poor prognostic factors, revealed that upfront osimertinib was associated with longer PFS1 but similar OS and PFSglob compared to the sequence group.

In our subgroup analysis, we investigated the benefit of upfront osimertinib in specific patient groups. Firstly, in patients with CNS involvement at diagnosis, our study demonstrated a higher 18-month PFS1 rate (53.5% *vs.* 27.6%). These findings are in line with previous reports (15,16). Indeed, the FLAURA trial reported a higher CNS response rate (91% *vs.* 68%) and a longer CNS-PFS (NR in 2018 *vs.* 13.9 months, P=0.01). Osimertinib plays a major role in CNS protection by delaying the onset of brain metastases in the first-line setting, providing a distinct advantage in this regard; however, in the absence of the CNS or in the presence of poor prognostic factors, first or second-generation TKIs may still have a role, especially in countries with limited access to third-generation TKIs (i.e., low-middle-income countries).

Liver metastases, known as a poor prognosis factor in m*EGFR* NSCLC, lacked specific results in the FLAURA trial (17,18). In our study, patients with liver metastasis had a dreadful prognosis, and upfront osimertinib demonstrated benefit in term of PFSglob (median 17.7 *vs.* 14.8 months) and PFS1 (median 15.3 *vs.* 9.7 months). Lastly, patients with poor PS experienced greater benefit from upfront osimertinib. All these findings suggest that patients with aggressive disease and poor prognosis factors at diagnostic may benefit from a more potent and intensified first-line treatment strategy (19).

Combinations with platinum-based chemotherapy in the FLAURA 2 trial (NCT04035486), and with lazertinib and amivantamab (NCT04487080) have recently demonstrated improved outcomes *vs.* osimertinib (9,10). First line PFS was 25.5 and 23.7 months, in the experimental arms of the FLAURA 2 and MARIPOSA trials, respectively. OS data are still pending for these trials, but we already have a signal for higher toxicity rates in both experimental arms. Moreover, combination of osimertinib with anti-angiogenic drugs (NCT04181060) could also provide interesting results compared with osimertinib alone in the first line setting. Our results support the fact that combination therapies could be an interesting option for patients with poor prognosis factors whereas, 1$^{st}$ and 2$^{nd}$ generation TKI could be prescribed in the specific subgroup of patients with low TB.

It is important to acknowledge limitations attributed to the retrospective design of our study. A notable limitation is the presence of selection bias, given that patients in the sequence arm were required to undergo two lines of treatment, a condition not applicable to the osimertinib group. To address this bias, a propensity score was generated for correction. Despite the limitation, this study represents the largest real world study in a European population exploring the potential advantages of upfront Osimertinib or as sequential therapy in advanced m*EGFR* NSCLC. Our results corroborate the one from Okuma *et al.* in an Asian population (19).

## Conclusions

In this retrospective international study involving 300 patients, we demonstrated the superiority of first-line osimertinib *vs.* a standard EGFR-TKI in term of PFS1. Additionally, our findings highlight the efficacy of osimertinib in the management of patients with poor prognosis factors (i.e., CNS, liver metastasis, poor PS). For patients with a low TB, the sequence strategy, involving osimertinib in the second-line setting, remains a viable option.

## Acknowledgments

This study was presented at the WCLC 2023 as a poster presentation (Volume 18, Issue 11, Supplement S344 November 2023). Permission has been obtained to reuse the abstract and Figure 1.

## Footnote

*Reporting Checklist*: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-881/rc

*Data Sharing Statement*: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-881/dss

*Peer Review File*: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-881/prf

*Funding*: This study was supported by the following research grants (awarded to L.M.): the Contrato Juan Rodes 2020 (JR20/00019; ISCIII, Ministry of Health); Ayuda de la Acción Estratégica en Salud-ISCIII FIS 2021 (PI21/01653);

 

Ayuda SEOM-Juan Rodés 2020.

*Conflicts of Interest*: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-881/coif). E.A. declared lectures and educational activities in Sanofi-Genzymes; consulting, advisory role in Amgen, Sanofi and travel, accommodations, expenses from Amgen, Ipsen. L.M. declared research grants from Amgen, Inivata, AstraZeneca, Gilead; lectures and educational activities in Bristol-Myers Squibb, AstraZeneca, Roche, Takeda, Janssen, Pfizer, MSD; consulting, advisory role in Roche, Takeda, AstraZeneca, Janssen, MSD; and travel, accommodations, expenses from Bristol-Myers Squibb, Roche, Takeda, AstraZeneca, Janssen. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. This study was approved by the internal ethics committee at Gustave Roussy (IRB number 2021-01) and in each center according to the local rules. No consent to participate was needed for participation as it is a retrospective study.



## References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
2. Remon J, Steuer CE, Ramalingam SS, et al. Osimertinib and other third-generation EGFR TKI in EGFR-mutant NSCLC patients. Ann Oncol 2018;29:i20-7.
3. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8.
4. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
5. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
6. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2017;376:629-40.
7. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
8. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020;382:41-50.
9. Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. N Engl J Med 2023;389:1935-48.
10. Cho BC, Felip E, Spira AI, et al. LBA14 Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Primary results from MARIPOSA, a phase III, global, randomized, controlled trial. Ann Oncol 2023;34:S1306.
11. Lorenzi M, Ferro A, Cecere F, et al. First-Line Osimertinib in Patients with EGFR-Mutant Advanced Non-Small Cell Lung Cancer: Outcome and Safety in the Real World: FLOWER Study. Oncologist 2022;27:87-e115.
12. Remon J, Besse B, Aix SP, et al. Osimertinib treatment based on plasma T790M monitoring in patients with EGFR-mutant non-small-cell lung cancer (NSCLC): EORTC Lung Cancer Group 1613 APPLE phase II randomized clinical trial. Ann Oncol 2023;34:468-76.
13. Hori T, Yamamoto K, Ito T, et al. Upfront Use of First-/Second-Generation EGFR-TKI Followed by Osimertinib Shows Better Prognosis than Upfront Osimertinib Therapy in Japanese Patients with Non-small-cell Lung Cancer with Exon 19 Deletion: A Single-Center Retrospective Study. Biol Pharm Bull 2023;46:788-95.
14. Luo FX, Arter ZL, Ou SI, et al. FLAURA in the real

world: osimertinib in potentially trial-eligible and ineligible patients with EGFR-mutated advanced non-small cell lung cancer. AME Clin Trials Rev 2024;2:101.
15. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2018. [Epub ahead of print]. doi: 10.1200/JCO.2018.78.3118.
16. Mosca M, Conci N, Di Federico A, et al. First-Generation Epidermal Growth Factor Receptor Inhibitors Plus Antiangiogenic Drugs Versus Third-Generation Epidermal Growth Factor Receptor Inhibitors in Advanced Non-Small-Cell Lung Cancer: A Meta-Analysis. JCO Precis Oncol 2023;7:e2300073.
17. Jiang T, Cheng R, Zhang G, et al. Characterization of Liver Metastasis and Its Effect on Targeted Therapy in EGFR-mutant NSCLC: A Multicenter Study. Clin Lung Cancer 2017;18:631-639.e2.
18. Castañón E, Rolfo C, Viñal D, et al. Impact of epidermal growth factor receptor (EGFR) activating mutations and their targeted treatment in the prognosis of stage IV non-small cell lung cancer (NSCLC) patients harboring liver metastasis. J Transl Med 2015;13:257.
19. Okuma Y, Shintani Y, Sekine I, et al. Efficacy of Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors in Metastatic Non-Small Cell Lung Cancer Patients with Poor Performance Status and Epidermal Growth Factor Receptor Mutations: Findings from the Japanese Lung Cancer Registry Database. Clin Lung Cancer 2024;25:336-346.e2.

**Cite this article as:** Auclin E, Du Rusquec P, Albarran-Artahona V, Aboubakar F, Gerber H, Epaillard N, Recondo G, De Giglio A, Berthou H, Laguna JC, Gorria T, Blaquier JB, Jimenez-Munarriz B, Tagliamento M, Di Federico A, Sacco G, Minatta J, Girard N, Moran-Bueno T, Lopez-Castro R, Besse B, Mezquita L. Upfront osimertinib and as sequential therapy in patients with *EGFR*-mutant non-small cell lung cancer (NSCLC): benefit across patients groups in a real-world retrospective cohort—the smile study. Transl Lung Cancer Res 2025;14(7):2427-2436. doi: 10.21037/tlcr-24-881